PERTUSSIS IMMUNIZATION BEFORE 24 WEEKS OF PREGNANCY

MATERNAL ANTIBODY TRANSFER, REACTOGENICITY AND ACCEPTANCE

MAARTEN IMMINK

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Pertussis Immunization
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Vaccinatie tegen kinkhoest
vóór 24 weken zwangerschap

maternale antistofoverdracht, bijwerkingen en acceptatie

(met een samenvatting in het Nederlands)

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CHAPTER 1

General introduction

Overview

Infant pertussis remains a major cause of hospitalizations and sometimes death in the first months of life, before protection is achieved upon primary vaccinations. Among older (fully) vaccinated children and healthy adults the disease generally manifests milder and less typical. However, both pertussis vaccination and the disease offer protection of limited duration. Therefore, pertussis is still endemic and vaccinated individuals have remained an important source of transmission of pertussis to newborns, despite high vaccination coverage worldwide. Infants too young to be vaccinated and particularly preterm infants are the most vulnerable for developing severe disease complications, leading to an overrepresentation of pertussis hospitalizations of preterms in many countries, e.g. 150% in the Netherlands. To prevent pertussis in young infants in the months before protection by vaccinations is achieved, many countries - including 28 in Europe - offer a maternal pertussis vaccination during pregnancy. This enhances production of maternal pertussis-specific antibodies, that are actively transferred across the placenta from mother to child. This strategy provides newborns about 90% protection against pertussis directly after birth until they are ready to receive primary infant vaccinations. Most countries encourage maternal vaccination in pregnant women between 28 and 32 weeks of gestational age, when transplacental antibody transfer is at a higher rate. However, this may be too late for sufficient transfer over time in case of premature delivery. Many studies have investigated the effects of maternal vaccination on the benefits for term infants. In contrast, evidence on timing of vaccination throughout pregnancy, particularly for protecting preterm infants, remains very scarce. For this reason, this thesis explores the effects of timing of maternal vaccination against pertussis during pregnancy, in particular for preterm infants, in order to investigate if a sufficient amount of antibodies is transferred to protect term and in particular preterm babies from clinical pertussis.

To this aim, we designed a longitudinal cohort study named '**P**remature **I**nfants and **M**aternal **P**ertussis **I**mmunization' (PIMPI). This study was conducted among pregnant women under primary, secondary and tertiary antenatal care in the Netherlands and covered three major aspects of maternal pertussis immunization, i.e. immunogenicity at different time points of maternal vaccination during pregnancy, reactogenicity of the vaccine and acceptance of maternal pertussis vaccination in the second versus third trimester, with special focus on potential benefits for preterm infants in case of second trimester ($20^{0/7}$-$24^{0/7}$ weeks of gestation) vaccination versus third trimester ($30^{0/7}$-$33^{0/7}$ weeks of gestation) vaccination. This thesis describes the results of the study, together with other

aspects that may contribute to the prevention of pertussis in early infancy through maternal immunization, e.g. the evaluation of immunization programs, pathogen circulation, vaccine safety, and targeting immunocompromised pregnant women.

Pertussis

Clinical manifestation

Pertussis, or whooping cough, is a highly contagious respiratory disease, caused mainly by the bacterium *Bordetella pertussis* and occasionally by *B. parapertussis*. *B. pertussis* may infiltrate respiratory epithelial cells, where it produces toxins that induce necrotic tissue damage, leading to the traditional cough.[1] After a short incubation period, a typical infection initiates with the catarrhal stage, that manifests with symptoms of a common cold or malaise. It is also the stage with the highest rate of transmission to others and holds a secondary attack rate of 90% to fellow household members without immunological protection.[2] Towards (yet) unvaccinated individuals, the basic reproduction number (R_0) for pertussis was estimated between 12-17.[3-5] The catarrhal stage lasts about 1-2 weeks and then progresses into the paroxysmal stage, that manifests in multiple consecutive coughs with a high-pitched “whoop”-sound during inhalation, often followed by vomiting. The cough gets gradually milder during the convalescent stage, although it may last several weeks or months until final recovery. Pertussis may be confirmed either directly (PCR or culture) or indirectly (serology), with the direct techniques most sensitive in the very early stages of disease and the indirect technique during later stages (Figure 1).[6] Previously infected persons may become susceptible for re-infection after approximately 4-20 years because of waning immunity.[7]

The severity of clinical pertussis symptoms ranges widely between individuals. In older children and healthy adults who have been usually infected before or have been vaccinated against pertussis, pertussis often manifests mildly and symptoms may even remain unrecognized. Nonetheless, immunocompromised adults, elderly, and especially infants who are too young to be vaccinated may suffer from more severe pertussis and complications due to absent, low and/or waning immunity, which may require hospitalization.[8-10] It is estimated that more than half of all infants who get infected under six months of age need hospitalization, with atypical presentations like apnea or cyanosis.[11-13] Especially preterm infants are vulnerable of severe disease, resulting into an overrepresentation in pertussis hospitalizations in many countries.[14,15] For instance in the Netherlands, more than 12% in the share of all hospitalized infants in the Netherlands are preterms, while they represent only 8% of the national birth cohorts.[16] Severe complications in this

group include secondary pneumonia, convulsions, respiratory failure and death.[17]

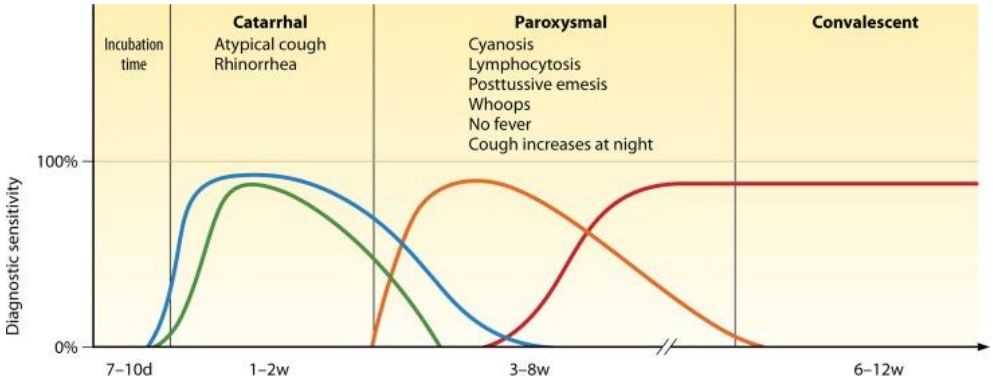


Figure 1. Relative diagnostic sensitivities of culture (green), PCR (blue), serology (red), and clinical diagnosis (orange) during different stages of a *B. pertussis* infection.[6]

Epidemiology and history of vaccination

Before the first pertussis vaccines became available in the 1950s, pertussis was a highly prevalent and lethal childhood disease that caused over 4000 deaths each year in the USA and around 375 deaths per year in the Netherlands, with incidence rates of 3.2/100,000 and 3.8/100,000, respectively.[18,19] The introduction of whole cell pertussis (wP) pediatric vaccination programs contributed to a more than 99% reduction in pertussis-related deaths worldwide.[18,20,21] The wP vaccine, that consists of inactivated and detoxified *B. pertussis* bacteria, was however quite reactogenic and adverse events became the center of attention after 20 years of immunization at the time of low pertussis incidence. In response to the concerns about the reactogenicity and safety of wP vaccination, acellular pertussis (aP) vaccines were developed and introduced in the nineties of the previous century in many countries in Europe and the USA. Most of the aP vaccines contain three or five purified antigens produced by *B. pertussis*, i.e. pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (Prn) and in some aP vaccines also fimbriae (FIM) 2 and 3. Acellular pertussis vaccines are much less reactogenic and induce similar to higher pertussis-specific antibody levels compared to wP vaccines after primary infant vaccinations.[22-25] Clinical trials also showed comparable or better vaccine efficacy in the first years after introduction.[26,27] It was later constated that the endurance of protection over time is shortened, which led to more symptomatic infections after aP compared with wP vaccination in adolescents.[28-30] Acellular pertussis vaccines also induce different cellular immunity than wP vaccines, showing less Th17 and Th1 activity that is relevant for clearance of the infectious agent and therefore the reduction of transmission.[31,32]

Despite the global vaccination effort targeting pertussis, the disease re-emerged in the late-nineties in many countries after a long period of low incidence despite steady and high vaccine coverage rates.[33-36] The cause for the resurgence was multifactorial and came with improved diagnostics, enhanced surveillance, pathogen adaptation over time and altered immunity after the switch from wP to aP vaccines.[31-34,37,38]

The Netherlands implemented several changes in the National Immunization Program (NIP) in response to the increase of pertussis in infancy. In 1999, the first infant wP vaccination was scheduled at two months of age instead of three months of age. In 2001, an aP vaccine - containing PT, FHA, Prn - was added to the combined diphtheria, tetanus and poliomyelitis preschool booster dose at four years of age, since these preschool children appeared often infected and a source for transmission to newborns. From 2005 onwards, an aP vaccine completely replaced the wP vaccines in the primary vaccination series with a combination vaccine that also included diphtheria, tetanus and polio. Nevertheless, the pertussis incidence in infants younger than five months of age failed to show a lasting decrease following these changes.[39] Nowadays, the disease is still endemic across all age groups and comes with epidemic peaks every 3-4 years in the Netherlands, in which young infants under 6 months of age account for the highest number of pertussis notifications and hospitalizations (Figure 2).[20,39,40] The most recent change in the Netherlands was the addition of a so called maternal vaccination in 2019, which can be administered to pregnant women from 22 weeks of gestational age until labor. The vaccine contains the acellular pertussis antigens of PT, FHA and Prn in combination with toxoids of tetanus and diphtheria and provides infants protection from birth until primary infant vaccinations.[41] More detailed information on the maternal vaccination principles is provided later on in this chapter.

Surveillance of the National Immunization Program

In the Netherlands, general surveillance of infectious diseases under the NIP consists of five pillars: 1) surveillance of vaccination uptake, 2) surveillance of safety, 3) disease surveillance, 4) pathogen surveillance and 5) immunosurveillance. These pillars together provide input for evaluating and, if necessary, improving the NIP, e.g. when new vaccination strategies are implemented. Nevertheless, surveillance of many infectious diseases and in particular pertussis remains suboptimal. For instance, registration of pertussis cases is mandatory for disease surveillance, however a clinical diagnosis depends on the awareness of general practitioners to recognize the disease, and may be

affected by the reluctance of the public to seek medical attention, particularly if the disease manifests mildly. Furthermore, laboratory confirmation, which is necessary for notification, is often not performed, because of additional costs and weak impact on the progression of disease. True incidence rates based on reported notifications are therefore severely underestimated.[13,42]

Many studies have investigated the circulation of *B. pertussis* globally by assessing serologic population-based antibody responses induced by a recent infection (pillar 5) in order to strengthen disease surveillance (pillar 3).[11,43-51] However, in many countries, insufficient laboratory facilities hamper case confirmation and thus, no information about the transmission of *B. pertussis* is available. It remains highly necessary to keep performing serosurveillance studies in these countries, as it may be the only way to track the circulation of *B. pertussis* and monitor the surveillance of pertussis. This may be the case on the islands that comprise the Caribbean Netherlands, i.e. Bonaire, St. Eustatius and Saba.

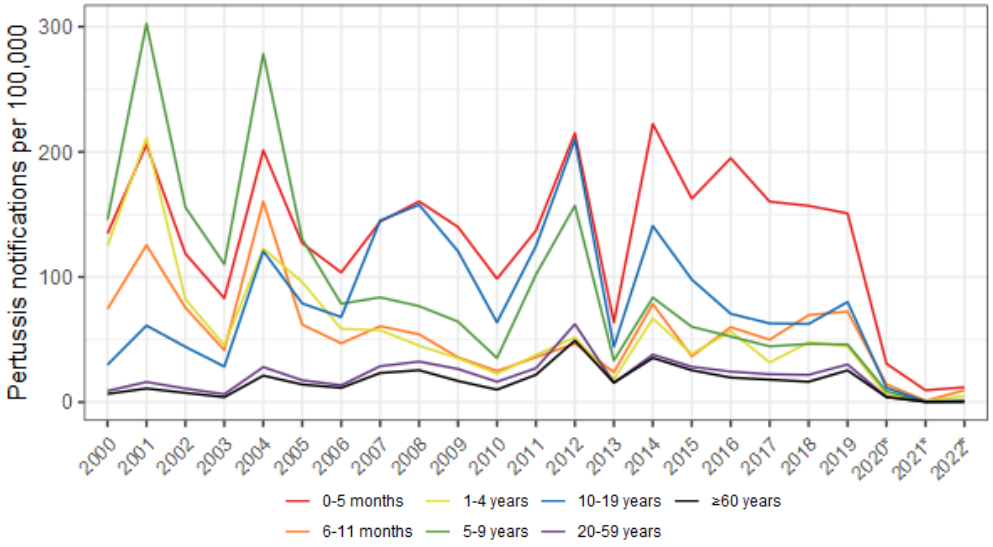


Figure 2. Number of pertussis notifications per 100,000 per age category in the Netherlands between 2000-2022.[52] *Notifications in 2020-2022 were lower presumably due to a relatively low transmission rate during the COVID-19 lockdown periods, similar to many other infectious diseases.[53]

Maternal immunization

Principles of maternal vaccination

Unvaccinated infants during the first months of life depend on maternal antibodies for protection against disease. Maternal IgG antibodies are transferred across the placenta, mediated by the neonatal Fc-receptor that is expressed by the

syncytiotrophoblast. This is a saturable process that initiates between 13-17 weeks gestational age (GA) and increases with time as the cytotrophoblast layer becomes discontinuous.[54] The process will also initiate active transfer later throughout pregnancy as infant antibody levels referred to their mothers' increase from 10% (17–22 weeks GA) to 50% (28–32 weeks GA), until they exceed maternal levels around 33-36 weeks (Figure 3).[55-57] Immunization of pregnant women with a tetanus, diphtheria and acellular pertussis (Tdap) vaccine enhances maternal IgG antibody levels against these three diseases in pregnant women so that more disease-specific antibodies are being transferred to their offspring. Subsequently, infants are provided with immunological protection from birth until they are old enough to receive protection following primary vaccinations.[58-61] In addition to this process, maternal vaccination offers secondary benefits to infants through breast milk IgG and IgA pertussis-specific antibodies and potentially through cocooning, although aP vaccines are claimed not to affect the clearance of infection and vaccinated persons may remain source of infection.[62-64] Nevertheless, cocooning still provides partial post-partum protection as the mother is less likely to be a source of transmission due to her acquired protection from recent vaccination.

Many studies have assessed the association between Tdap vaccination during pregnancy and the prevention of clinical pertussis under the age of three months in term born babies, with infants' primary vaccination series often at two or three months. These studies concluded that maternal Tdap vaccine effectiveness ranges consistently between 85% and 95%.[65-71] In addition, the maternal Tdap vaccination is found safe, and it is confirmed that no increased risks of any adverse (pregnancy related) outcomes are observed in women or their offspring after maternal Tdap vaccination.[72-76] Putting these findings together resulted into many countries - including 28 in Europe – having enrolled a strategy to offer a pertussis-containing vaccination to women during pregnancy.[77]

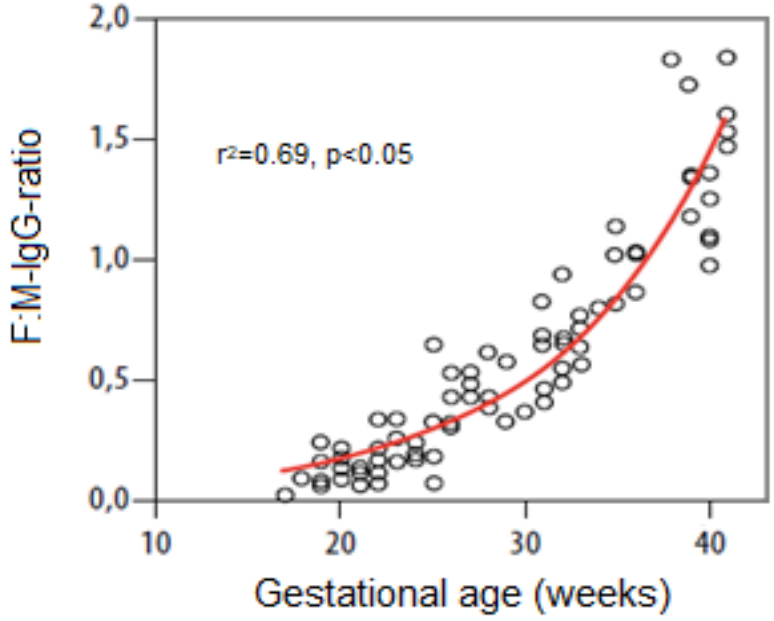


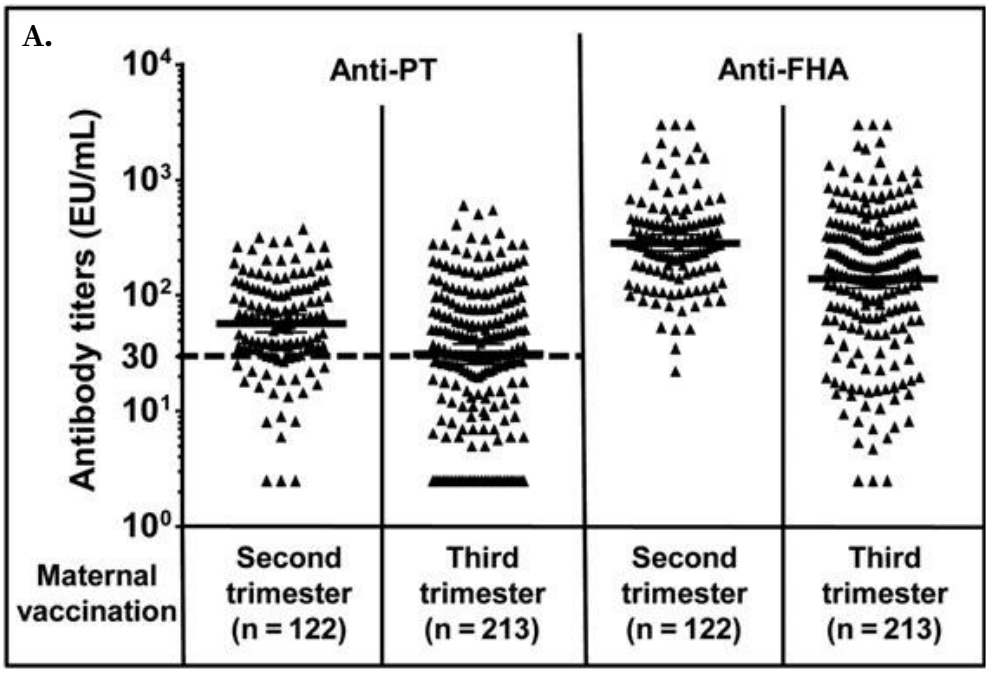
Figure 3. Fetal-to-maternal ratio of IgG antibody levels related to gestational age.[55]

Timing of maternal vaccination during pregnancy

The most dominant antigen responsible for the burden of pertussis in young infants is pertussis toxin.[78,79] Achieving optimal antibody levels against PT in infants after birth depends on multiple factors; antibody levels post-vaccination in mothers, pregnancy duration, time interval between vaccination and delivery, placental function, vaccine type and maternal health status and the type of anti-pertussis vaccination series the mother received during infancy; wP vaccines seem to induce higher boosting and transfer effects against pertussis during childbearing age compared with aP vaccines.[55,80] Tdap vaccine-induced antibodies within this group of women generally approach peak levels 12-28 days post-vaccination, and decay gradually with time.[81] With the knowledge that the overall transfer rate is the highest at the end of the third trimester, a Swiss randomized trial investigated umbilical cord sera for anti-PT and FHA IgG levels after second trimester (i.e. 13-25 weeks GA) vs third trimester (i.e. ≥26 weeks GA) Tdap vaccination in term-born babies.[82] The authors concluded that second rather than third trimester vaccination optimized term infant antibody levels (e.g. mean for anti-PT: 57.1 vs 31.1 ELISA units/mL, respectively, $p<0.001$) which was postulated to be due to a longer interval between vaccination and delivery (Figure 4A). However, when stratifying for GA at vaccination, infant antibody levels rose gradually with later maternal vaccine administration until they peaked at 30-33 weeks GA, after which

they steeply declined with a shorter interval between vaccination and delivery (Figure 4B). As these strata were small, the authors cautiously interpreted that a maternal Tdap vaccination should be administered between 13-33 weeks GA, assuming a full-term delivery. A later study among term infants from mothers who were vaccinated between 27-36 weeks GA concluded that a Tdap vaccination should be administered early in the third trimester, as PT IgG antibody levels in full-term cord sera were highest if mothers were vaccinated around 27-30 and peaked at 30 weeks GA.[83]

While there is still quite some controversy about optimal timeliness of maternal vaccination regarding term infants, evidence for preterm infants remains very scarce. Thus far, two studies suggested that earlier Tdap vaccination throughout pregnancy may be preferred over later vaccination in order to enhance anti-PT levels in preterm infants at birth.[84,85] A longer time interval between maternal vaccination and delivery resulted in higher antibody levels in cord sera from preterm infants, but overall antibody levels remained lower compared to full-term infants. These studies were however limited to vaccination from ≥$24^{0/7}$ weeks GA,[84] or studied a very small sample size (n=9).[85] To gain more insight on maternal vaccination timing regarding preterm infants, we designed a longitudinal cohort study named '**P**remature **I**nfants and **M**aternal **P**ertussis **I**mmunization' (PIMPI), in which several aspects of maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$ weeks GA were investigated in pregnant women. The PIMPI-study primarily assessed antibody levels against all Tdap-included antigens in a large group of 221 preterm and full-term mother-infant-pairs after maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$ weeks GA.



B.

Gestational Week at Maternal Vaccination	No. (%)	Anti-PT GMC (95% CI)	Anti-FHA GMC (95% CI)
39–41	21 (6)	9.0 (5.0–16.2)	31.0 (16.9–56.6)
37–38	74 (22)	25.1 (17.9–35.3)	92.7 (69.0–124.7)
34–36	72 (22)	32.7 (24.1–44.3)	173.0 (126.5–236.6)
30–33	16 (5)	74.9 (38.3–146.4)	417.3 (232.7–748.4)
26–29	30 (9)	70.3 (49.0–100.8)	376.8 (257.0–552.7)
22–25	54 (16)	68.3 (52.8–88.3)	291.8 (222.8–382.2)
17–21	42 (13)	53.1 (37.2–75.7)	267.3 (205.4–347.9)
13–16	26 (8)	44.2 (32.2–60.7)	297.9 (206.7–429.4)

Figure 4. Individual concentrations (panel A) and geometric mean concentrations (GMCs) (panel B) for anti–PT and anti–FHA in cord sera by trimester or GA at maternal Tdap vaccination.[82] The dotted line indicates the arbitrary cutoff for expected infant seropositivity according to Eberhardt et al. (anti-PT = 30 enzyme-linked immunosorbent assay units expressed in EU/mL). GMCs and 95% confidence intervals (95% CIs) are indicated for the different strata for GA at maternal Tdap vaccination.

Current maternal vaccination strategy in the Netherlands

Apart from optimizing immunogenicity and transplacental antibody transfer, preventing pertussis in early preterm and full-term infancy through maternal immunization comes with many other challenges. First, the willingness of pregnant women to accept the vaccination depends on many factors, i.e. data on effectiveness and perceived safety,[86-89] perceived risk of disease susceptibility and severity,[87,88] attitude of women's healthcare professional towards maternal Tdap

immunization,[86,87,89-94] and logistical matters for obtaining the vaccine.[95] All these factors together require a well-established enrollment strategy for offering a vaccine to pregnant women. In the Netherlands, the maternal Tdap vaccination was introduced as part of the NIP in December 2019 and is now offered to all pregnant women from 22 weeks GA onwards until labor. One of the reasons for such a wide time interval is that it offers women a better opportunity to obtain the vaccine, which previously led to an increase of vaccine coverage in England of about 15%.[96,97] Nonetheless, a high vaccination coverage does not necessarily mean that the entire population is well-protected as the optimal timing for maternal vaccination is unknown. Studies showed that women in their second trimester are less willing to accept a maternal Tdap vaccination compared to women later throughout gestation.[98,99] However, these studies were performed without the knowledge that second-trimester maternal vaccination provides more time for transplacental antibody transfer, and some studies point to increased protection against pertussis as a result of an enlarged time interval between vaccination and delivery.[82] Therefore, it is important to investigate if the determinants that underlie Tdap vaccine acceptance in the second trimester of pregnancy changed due to this new information.

As for logistical matters, antenatal care providers are supposed to make pregnant women aware of the maternal Tdap vaccination and hand out an information package. Women are then referred to a youth healthcare facility for more counseling (if requested) and for Tdap vaccination. Before the corona pandemic, up till 2019, this strategy resulted in a vaccine coverage that ranges around 70%[52,100] In Flanders, Belgium, the current maternal Tdap vaccine coverage ranges around 85%. It is known that apart from the pregnant women, the attitude of healthcare professionals towards maternal Tdap immunization also contributes to vaccine uptake.[86,87,89-94] Therefore, in order to provide insight for refining the current protocol and possibly how to increase vaccine uptake, the process of vaccine implementation and its execution from antenatal care providers' perspective shortly after the maternal Tdap inclusion in December 2019 needs evaluation.

Another challenge is that implementations of new vaccinations require extensive reactogenicity and safety monitoring, particularly when targeting new and/or vulnerable populations such as pregnant women (pillar 2 of surveillance of the NIP). Widespread safety concerns may hamper attitudes towards vaccination, probably resulting in a decrease of the vaccination coverage.[101,102] It has to be noted that not all adverse outcomes that follow shortly after immunization necessarily implicate a causal relation to the vaccine, as the timing of a reaction following

immunization may also be due to coincidence.[103] Nevertheless, public safety signals must be taken seriously, even though the vaccination is considered well-tolerated and safe for utilization in pregnant women. This evidence though is mainly based on third trimester vaccination.[104-107] The reactogenicity and safety of second-trimester Tdap vaccination has yet to be evaluated in the Netherlands since offering the vaccine to all pregnant women is ongoing since 2019, and safety-related concerns must be compared to third trimester Tdap vaccination. Furthermore, the baseline incidence rates of adverse pregnancy outcomes in the years prior to the maternal Tdap vaccination implementation in 2019 in the Netherlands need to be mapped, in order to put into perspective the safety concerns that may rise in the years following the implementation.

It must also be considered that maternal vaccine implementations may have consequences for neonatal vaccine schedules. In the Netherlands, a maternal Tdap vaccination replaces the first infant vaccination for term infants who may then be vaccinated at 3, 5 and 11 months of age with a DTaP-IPV-Hib-HepB vaccine. Preterm infants are excluded from this reduced and postponed schedule and receive an extra DTaP-IPV-Hib-HepB vaccination between 6-9 weeks of age. Based on the results of the PIMPI-study, we should evaluate – for term-borns and preterm-borns separately – whether the adapted vaccine schedule remains necessary for preterms, or that maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA induces sufficient antibody levels in infants so that the reduced 2+1 schedule may also be feasible. As preterm infants as a whole regarding undergo different stages maternal antibody transfer during pregnancy, and the majority of preterms is born after 32w GA, we divided this group in early-preterms (born $<32^{0/7}$ weeks GA) or late-preterm infants (born $\geq 32^{0/7}$ weeks GA) in order to investigate the benefits from second trimester Tdap vaccination adjusted for the gestational age at which the infant is born.

Other questions concern targeting specific (sub)-populations that may not be fully protected by maternal vaccination. The effects of Tdap vaccination during pregnancy may be impaired when the mother gets treatment with biological disease-modifying antirheumatic drugs (bDMARDs), e.g. for rheumatic disease. It is presumed that fewer IgG antibodies are transferred to infants as bDMARDs may hamper the maternal immune response to vaccines.[108,109] To date, no evidence about vaccine responses during pregnancy and subsequent IgG antibody transfer following immune-modulating therapy during pregnancy is available and it is unknown if any additional (vaccine) measures targeting this group are required.

Aims of this thesis

This thesis describes the transplacental transfer of pertussis-specific antibodies in preterm and full-term infants through second trimester (between $20^{0/7}$-$24^{0/7}$weeks GA) maternal immunization. In Part I, we aim to describe the immunogenicity of maternal Tdap vaccination before 24 weeks GA regarding term and preterm infants, how specific vulnerable populations should be targeted, and the safety of the vaccine. Part II of this thesis describes the social and psychological aspects of maternal immunization as a Public Health intervention. We report on socio-psychological determinants that may underlie vaccine acceptance, and we evaluate the maternal Tdap vaccination implementation as part of the National Immunization Program from antenatal care providers' point of view), including several aspects that may influence the vaccination strategy. Within these two parts, we specified our research objectives as follows, in order to:

- evaluate the current maternal and infant vaccination guidelines through
    - investigating the differences in neonatal IgG antibody levels against pertussis up to two months after preterm and full-term birth in infants born to mothers who were Tdap vaccinated between $20^{0/7}$-$24^{0/7}$weeks GA.
    - investigating the differences in neonatal IgG antibody levels against pertussis up to two months after full-term birth in infants born to second vs third trimester Tdap vaccinated mothers.
    - assessing Tdap vaccine responses in immunocompromised pregnant women and determine whether transplacental IgG antibody transfer is hampered.
    - evaluating the reactogenicity and safety of second vs third trimester maternal Tdap vaccination.
    - putting into perspective legitimate safety concerns regarding maternal Tdap vaccination that may possibly rise in the near future.
    - gaining insight on *B. pertussis* circulation on the islands of CN by relating serosurveillance to local disease surveillance.
- further improve communication on the current maternal Tdap vaccination strategy to professionals and public by
    - identifying pregnant women's sociopsychological factors that influence vaccine acceptance during the second trimester of pregnancy.
    - evaluating the implementation of the maternal Tdap vaccination from the perspective of the antenatal care providers.

Outline of this thesis

Part I

Chapter 2 describes the design of the PIMPI-study. We provided the rationale for the study and its objectives, details on study procedures, inclusion criteria, sample size calculations and methods for statistical analyses. In **Chapter 3**, IgG antibody levels against all Tdap-included antigens in preterm and full-term infants up to two months after birth were assessed, where infants were born to mothers who were Tdap vaccinated between $20^{0/7}$-$24^{0/7}$ weeks GA. We referred our data to a historical comparator cohort of mothers and their offspring, who received a maternal Tdap vaccination between $30^{0/7}$-$33^{0/7}$ weeks GA.[110] **Chapter 4** describes post-hoc analyses of the aforementioned immunogenicity study presented in a brief report, focusing on antibody transfer to early vs late preterms, here defined as $<32^{0/7}$ weeks vs $\geq 32^{0/7}$ weeks GA, respectively. In addition, the decay rates for maternal antibodies in the first two months after birth were estimated. In **Chapter 5**, antibody levels in vaccinated pregnant women on immune-modulating treatment for rheumatic disease are described. Vaccine responses and transplacental antibody transfer rates were assessed for pregnant patients exposed vs unexposed to bDMARDs, while ultimately referring to healthy controls. **Chapter 6** describes reactogenicity of second trimester immunization in a questionnaire study that we compared to similar data of the abovementioned historical comparator cohort.[110] In addition, we referred safety data from the population of Tdap vaccinated questionnaire responders to data from the Dutch perinatal registry (DPR) consisting mainly of (presumably) unvaccinated pregnant women in 2018. To emphasize the safety of maternal Tdap vaccination, **Chapter 7** describes a retrospective cross-sectional study that assessed the baseline incidence of maternal and neonatal adverse pregnancy outcomes between 2006-2018, as derived from the DPR.[111] We can use these incidences in the near future to put into perspective any safety concerns that may rise in the years following the inclusion of the maternal Tdap vaccination in the Netherlands in December 2019. Lastly in **Chapter 8**, a seroepidemiological study on *Bordetella pertussis* circulation on the islands of the CN was presented with estimations on how serosurveillance relates to disease surveillance. Secondly, we identified factors that may contribute to the risk of (asymptomatic) infection.

Part II

In **Chapter 9**, we describe a prospective questionnaire study, in which we identified the determinants that underlie acceptance or rejection of second-trimester maternal Tdap vaccination among pregnant women. To evaluate the

maternal Tdap vaccine inclusion under the immunization program in the Netherlands in December 2019, we performed a quantitative (**Appendix**) and a qualitative study (**Chapter 10**) among healthcare personnel providing antenatal care. First, we assessed attitudes regarding maternal vaccination and their underlying factors in a questionnaire study among antenatal care providers (manuscript written and published in Dutch). Subsequently, we conducted semi-structured interviews with a random selection of questionnaire responders in order to evaluate their attitudes towards maternal vaccination. Finally in **Chapter 11**, we summarize and discuss the main findings that were presented in this thesis, as well as our recommendations for optimizing maternal or infant vaccine schedules targeting pertussis.

References

1. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8 ed; 2015.
2. Hodder SL, Mortimer EA, Jr. Epidemiology of pertussis and reactions to pertussis vaccine. *Epidemiol Rev* 1992; **14**: 243-67.
3. Anderson RM, May RM. Directly transmitted infections diseases: control by vaccination. *Science* 1982; **215**(4536): 1053-60.
4. Guerra FM, Bolotin S, Lim G, et al. The basic reproduction number (R(0)) of measles: a systematic review. *Lancet Infect Dis* 2017; **17**(12): e420-e8.
5. Gani R, Leach S. Transmission potential of smallpox in contemporary populations. *Nature* 2001; **414**(6865): 748-51.
6. van der Zee A, Schellekens JF, Mooi FR. Laboratory Diagnosis of Pertussis. *Clin Microbiol Rev* 2015; **28**(4): 1005-26.
7. Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. *Pediatr Infect Dis J* 2005; **24**(5 Suppl): S58-61.
8. Kandeil W, Atanasov P, Avramioti D, Fu J, Demarteau N, Li X. The burden of pertussis in older adults: what is the role of vaccination? A systematic literature review. *Expert Rev Vaccines* 2019; **18**(5): 439-55.
9. Edwards K, Freeman DM. Adolescent and adult pertussis: disease burden and prevention. *Curr Opin Pediatr* 2006; **18**(1): 77-80.
10. Rothstein E, Edwards K. Health burden of pertussis in adolescents and adults. *Pediatr Infect Dis J* 2005; **24**(5 Suppl): S44-7.
11. de Greeff SC, de Melker HE, van Gageldonk PG, et al. Seroprevalence of pertussis in The Netherlands: evidence for increased circulation of Bordetella pertussis. *PLoS One* 2010; **5**(12): e14183.
12. Kilgore PE, Salim AM, Zervos MJ, Schmitt HJ. Pertussis: Microbiology, Disease, Treatment, and Prevention. *Clin Microbiol Rev* 2016; **29**(3): 449-86.
13. van der Maas NAT, Hoes J, Sanders EAM, de Melker HE. Severe underestimation of pertussis related hospitalizations and deaths in the Netherlands: A capture-recapture analysis. *Vaccine* 2017; **35**(33): 4162-6.
14. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. *Arch Dis Child* 2017.
15. Riise OR, Laake I, Vestrheim D, et al. Risk of Pertussis in Relation to Degree of Prematurity in Children Less Than 2 Years of Age. *Pediatr Infect Dis J* 2017; **36**(5): e151-e6.
16. van der Maas NAT, Sanders EAM, Versteegh FGA, Baauw A, Westerhof A, de Melker HE. Pertussis hospitalizations among term and preterm infants: clinical course and vaccine effectiveness. *BMC Infect Dis* 2019; **19**(1): 919.
17. Vegelin AL, van Vught AJ, Wolfs TF, Kimpen JL, Geelen SP. [Pertussis in young infants]. *Ned Tijdschr Geneeskd* 1998; **142**(49): 2657-60.
18. Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working G. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 2007; **298**(18): 2155-63.
19. van Wijhe M, McDonald SA, de Melker HE, Postma MJ, Wallinga J. Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis. *Lancet Infect Dis* 2016; **16**(5): 592-8.
20. Schurink-van 't Klooster TM. the National Immunisation Programme in the Netherlands; surveillance and developments in 2015-2016. Bilthoven: National Institute for Public Health and the Environment, 2016.
21. van Wijhe M, McDonald SA, de Melker HE, Postma MJ, Wallinga J. Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis. *Lancet Infect Dis* 2016.
22. Hendrikx LH, Berbers GA, Veenhoven RH, Sanders EA, Buisman AM. IgG responses after booster vaccination with different pertussis vaccines in Dutch children 4 years of age: effect of vaccine antigen content. *Vaccine* 2009; **27**(47): 6530-6.
23. Hendrikx LH, Ozturk K, de Rond LG, et al. Identifying long-term memory B-cells in vaccinated children despite waning antibody levels specific for Bordetella pertussis proteins. *Vaccine* 2011; **29**(7): 1431-7.

24. van der Lee S, Stoof SP, van Ravenhorst MB, et al. Enhanced Bordetella pertussis acquisition rate in adolescents during the 2012 epidemic in the Netherlands and evidence for prolonged antibody persistence after infection. *Euro Surveill* 2017; **22**(47).
25. van der Lee S, van Rooijen DM, de Zeeuw-Brouwer ML, et al. Robust Humoral and Cellular Immune Responses to Pertussis in Adults After a First Acellular Booster Vaccination. *Front Immunol* 2018; **9**: 681.
26. Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med* 1996; **334**(6): 349-55.
27. Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Ad Hoc Group for the Study of Pertussis Vaccines. *Lancet* 1997; **350**(9091): 1569-77.
28. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap Effectiveness in Adolescents. *Pediatrics* 2016; **137**(3): e20153326.
29. Sheridan SL, Ware RS, Grimwood K, Lambert SB. Number and order of whole cell pertussis vaccines in infancy and disease protection. *JAMA* 2012; **308**(5): 454-6.
30. Witt MA, Arias L, Katz PH, Truong ET, Witt DJ. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccines in a large US cohort. *Clin Infect Dis* 2013; **56**(9): 1248-54.
31. Warfel JM, Merkel TJ. Bordetella pertussis infection induces a mucosal IL-17 response and long-lived Th17 and Th1 immune memory cells in nonhuman primates. *Mucosal Immunol* 2013; **6**(4): 787-96.
32. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci U S A* 2014; **111**(2): 787-92.
33. Cherry JD. Epidemic pertussis in 2012--the resurgence of a vaccine-preventable disease. *N Engl J Med* 2012; **367**(9): 785-7.
34. de Melker HE, Schellekens JFP, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MAE. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. *Emerg Infect Dis* 2000; **6**(4): 348-57.
35. Grant CC, Reid S. Pertussis continues to put New Zealand's immunisation strategy to the test. *N Z Med J* 2010; **123**(1313): 46-61.
36. Moerman L, Leventhal A, Slater PE, Anis E, Yishai R, Marva E. The re-emergence of pertussis in Israel. *Isr Med Assoc J* 2006; **8**(5): 308-11.
37. Mooi FR, Van Der Maas NA, De Melker HE. Pertussis resurgence: waning immunity and pathogen adaptation - two sides of the same coin. *Epidemiol Infect* 2014; **142**(4): 685-94.
38. van der Lee S, Sanders EAM, Berbers GAM, Buisman AM. Whole-cell or acellular pertussis vaccination in infancy determines IgG subclass profiles to DTaP booster vaccination. *Vaccine* 2018; **36**(2): 220-6.
39. van der Maas NAT, Mooi FR, de Greeff SC, Berbers GAM, Conyn-Spaendonck MAE, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? *Vaccine* 2013; **31**(41): 4541-7.
40. Meeting of the Strategic Advisory Group of Experts on immunization. Geneva: World Health Organization (WHO), 2014.
41. Boostrix ®, Official Product Information. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Boostrix/pdf/BOOSTRIX.PDF.
42. Barkoff AM, Grondahl-Yli-Hannuksela K, He Q. Seroprevalence studies of pertussis: what have we learned from different immunized populations. *Pathog Dis* 2015; **73**(7).
43. de Melker HE, Versteegh FG, Schellekens JF, Teunis PF, Kretzschmar M. The incidence of Bordetella pertussis infections estimated in the population from a combination of serological surveys. *J Infect* 2006; **53**(2): 106-13.
44. Versteegen P, Berbers GAM, Smits G, et al. More than 10 years after introduction of an acellular pertussis vaccine in infancy: a cross-sectional serosurvey of pertussis in the Netherlands. *Lancet Reg Health Eur* 2021; **10**: 100196.
45. Pebody RG, Gay NJ, Giammanco A, et al. The seroepidemiology of Bordetella pertussis infection in Western Europe. *Epidemiol Infect* 2005; **133**(1): 159-71.

46. Launay O, Toneatti C, Bernede C, et al. Antibodies to tetanus, diphtheria and pertussis among healthy adults vaccinated according to the French vaccination recommendations. *Hum Vaccin* 2009; **5**(5): 341-6.
47. Ronn PF, Dalby T, Simonsen J, Jorgensen CS, Linneberg A, Krogfelt KA. Seroepidemiology of pertussis in a cross-sectional study of an adult general population in Denmark. *Epidemiol Infect* 2014; **142**(4): 729-37.
48. Cattaneo LA, Reed GW, Haase DH, Wills MJ, Edwards KM. The seroepidemiology of Bordetella pertussis infections: a study of persons ages 1-65 years. *J Infect Dis* 1996; **173**(5): 1256-9.
49. Strebel P, Nordin J, Edwards K, et al. Population-based incidence of pertussis among adolescents and adults, Minnesota, 1995-1996. *J Infect Dis* 2001; **183**(9): 1353-9.
50. Baughman AL, Bisgard KM, Edwards KM, et al. Establishment of diagnostic cutoff points for levels of serum antibodies to pertussis toxin, filamentous hemagglutinin, and fimbriae in adolescents and adults in the United States. *Clin Diagn Lab Immunol* 2004; **11**(6): 1045-53.
51. Scott S, van der Sande M, Faye-Joof T, et al. Seroprevalence of pertussis in the Gambia: evidence for continued circulation of bordetella pertussis despite high vaccination rates. *Pediatr Infect Dis J* 2015; **34**(4): 333-8.
52. Pluijmaekers AJM, de Melker HE. The National Immunisation Programme in the Netherlands: Surveillance and Developments in 2020-2021: National Institute for Public Health and the Environment, 2021.
53. Middeldorp M, van Lier A, van der Maas N, et al. Short term impact of the COVID-19 pandemic on incidence of vaccine preventable diseases and participation in routine infant vaccinations in the Netherlands in the period March-September 2020. *Vaccine* 2021; **39**(7): 1039-43.
54. Ciobanu AM, Dumitru AE, Gica N, Botezatu R, Peltecu G, Panaitescu AM. Benefits and Risks of IgG Transplacental Transfer. *Diagnostics (Basel)* 2020; **10**(8).
55. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; **36**(5): 248-55.
56. Gitlin D. Development and metabolism of the immunoglobulins. . In: Stiehm. BKaE, ed. Immunologic Incompetence. Chicago: Book Medical Publishers; 1971: pp 3–13.
57. Saji F, Samejima Y, Kamiura S, Koyama M. Dynamics of immunoglobulins at the feto-maternal interface. *Rev Reprod* 1999; **4**(2): 81-9.
58. Kandeil W, van den Ende C, Bunge EM, Jenkins VA, Ceregido MA, Guignard A. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. *Expert Rev Vaccines* 2020; **19**(7): 621-38.
59. Lindley MC, Kahn KE, Bardenheier BH, et al. Vital Signs: Burden and Prevention of Influenza and Pertussis Among Pregnant Women and Infants - United States. *MMWR Morb Mortal Wkly Rep* 2019; **68**(40): 885-92.
60. Omer SB, Clark DR, Aqil AR, et al. Maternal Influenza Immunization and Prevention of Severe Clinical Pneumonia in Young Infants: Analysis of Randomized Controlled Trials Conducted in Nepal, Mali and South Africa. *Pediatr Infect Dis J* 2018; **37**(5): 436-40.
61. Regan AK, Munoz FM. Efficacy and safety of influenza vaccination during pregnancy: realizing the potential of maternal influenza immunization. *Expert Rev Vaccines* 2021; **20**(6): 649-60.
62. Maertens K, De Schutter S, Braeckman T, et al. Breastfeeding after maternal immunisation during pregnancy: providing immunological protection to the newborn: a review. *Vaccine* 2014; **32**(16): 1786-92.
63. Wiley KE, Zuo Y, Macartney KK, McIntyre PB. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. *Vaccine* 2013; **31**(4): 618-25.
64. Visser O, Kraan J, Akkermans R, et al. Assessing determinants of the intention to accept a pertussis cocooning vaccination: A survey among Dutch parents. *Vaccine* 2016; **34**(39): 4744-51.
65. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. *Arch Dis Child* 2018; **103**(3): 224-9.
66. Amirthalingam G, Campbell H, Ribeiro S, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. *Clin Infect Dis* 2016; **63**(suppl 4): S236-S43.
67. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014.

68. Dabrera G, Amirthalingam G, Andrews N, et al. A Case-Control Study to Estimate the Effectiveness of Maternal Pertussis Vaccination in Protecting Newborn Infants in England and Wales, 2012-2013. *Clin Infect Dis* 2014.
69. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of prenatal versus postpartum Tdap vaccination in preventing infant pertussis. *Clin Infect Dis* 2016.
70. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. *Pediatrics* 2017; **139**(5).
71. Bellido-Blasco J, Guiral-Rodrigo S, Miguez-Santiyan A, Salazar-Cifre A, Gonzalez-Moran F. A case-control study to assess the effectiveness of pertussis vaccination during pregnancy on newborns, Valencian community, Spain, 1 March 2015 to 29 February 2016. *Euro Surveill* 2017; **22**(22).
72. DeSilva M, Vazquez-Benitez G, Nordin JD, et al. Tdap Vaccination During Pregnancy and Microcephaly and Other Structural Birth Defects in Offspring. *JAMA* 2016; **316**(17): 1823-5.
73. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. *JAMA* 2014; **312**(18): 1897-904.
74. Shakib JH, Korgenski K, Sheng X, Varner MW, Pavia AT, Byington CL. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: pregnancy and infant health outcomes. *J Pediatr* 2013; **163**(5): 1422-6 e1-4.
75. Zheteyeva YA, Moro PL, Tepper NK, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. *Am J Obstet Gynecol* 2012; **207**(1): 59 e1-7.
76. Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA* 2014; **311**(17): 1760-9.
77. Maltezou HC, Effraimidou E, Cassimos DC, et al. Vaccination programs for pregnant women in Europe, 2021. *Vaccine* 2021; **39**(41): 6137-43.
78. Abu-Raya B, Forsyth K, Halperin SA, et al. Vaccination in Pregnancy against Pertussis: A Consensus Statement on Behalf of the Global Pertussis Initiative. *Vaccines (Basel)* 2022; **10**(12).
79. Scanlon K, Skerry C, Carbonetti N. Association of Pertussis Toxin with Severe Pertussis Disease. *Toxins (Basel)* 2019; **11**(7).
80. Havers FP, Skoff TH, Rench MA, et al. Maternal Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccination During Pregnancy: Impact on Infant Anti-Pertussis Antibody Concentrations by Maternal Pertussis Priming Series. *Clin Infect Dis* 2023; **76**(3): e1087-e93.
81. Halperin BA, Morris A, Mackinnon-Cameron D, et al. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. *Clin Infect Dis* 2011; **53**(9): 885-92.
82. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *Clin Infect Dis* 2016; **62**(7): 829-36.
83. Healy CM, Rench MA, Swaim LS, et al. Association Between Third-Trimester Tdap Immunization and Neonatal Pertussis Antibody Concentration. *JAMA* 2018; **320**(14): 1464-70.
84. Maertens K, Orije MRP, Herzog SA, et al. Pertussis immunization during pregnancy: assessment of the role of maternal antibodies on immune responses in term and preterm born infants. *Clin Infect Dis* 2021.
85. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization. *Clin Infect Dis* 2017; **64**(8): 1129-32.
86. Varan AK, Esteves-Jaramillo A, Richardson V, Esparza-Aguilar M, Cervantes-Powell P, Omer SB. Intention to accept Bordetella pertussis booster vaccine during pregnancy in Mexico City. *Vaccine* 2014; **32**(7): 785-92.
87. Hill L, Burrell B, Walls T. Factors influencing women's decisions about having the pertussis-containing vaccine during pregnancy. *J Prim Health Care* 2018; **10**(1): 62-7.
88. Hayles EH, Cooper SC, Sinn J, Wood N, Leask J, Skinner SR. Pertussis vaccination coverage among Australian women prior to childbirth in the cocooning era: a two-hospital, cross-sectional survey, 2010 to 2013. *Aust N Z J Obstet Gynaecol* 2016; **56**(2): 185-91.
89. Ko HS, Jo YS, Kim YH, et al. Knowledge and Acceptability about Adult Pertussis Immunization in Korean Women of Childbearing Age. *Yonsei Med J* 2015; **56**(4): 1071-8.

90. Winslade CG, Heffernan CM, Atchison CJ. Experiences and perspectives of mothers of the pertussis vaccination programme in London. *Public Health* 2017; **146**: 10-4.
91. McQuaid F, Jones C, Stevens Z, et al. Factors influencing women's attitudes towards antenatal vaccines, group B Streptococcus and clinical trial participation in pregnancy: an online survey. *BMJ Open* 2016; **6**(4): e010790.
92. O'Shea A, Cleary B, McEntee E, et al. To vaccinate or not to vaccinate? Women's perception of vaccination in pregnancy: a qualitative study. *BJGP Open* 2018; **2**(2): bjgpopen18X101457.
93. Bodeker B, Walter D, Reiter S, Wichmann O. Cross-sectional study on factors associated with influenza vaccine uptake and pertussis vaccination status among pregnant women in Germany. *Vaccine* 2014; **32**(33): 4131-9.
94. Laenen J, Roelants M, Devlieger R, Vandermeulen C. Influenza and pertussis vaccination coverage in pregnant women. *Vaccine* 2015; **33**(18): 2125-31.
95. Campbell H VHA, Bedford H, Craig L, Yeowell A-L, Green D, Yarwood J, Ramsay M, Amirthalingam G. Attitudes to immunisation in pregnancy among women in the UK targeted by such programmes. *British Journal of Midwifery* 2015; **Vol 23, No 8**.
96. Amirthalingam G, Brown CS, Campbell H, Chand MA, Fry NK. New Public Health England guidelines for managing pertussis in England. *J Infect* 2017; **74**(2): 202-4.
97. Pertussis vaccination programme for pregnant women update: vaccine coverage in England, April to June 2018: Public Health England, 2018.
98. van Lier A, Steens A, Ferreira JA, van der Maas NA, de Melker HE. Acceptance of vaccination during pregnancy: experience with 2009 influenza A (H1N1) in the Netherlands. *Vaccine* 2012; **30**(18): 2892-9.
99. Healy CM, Rench MA, Montesinos DP, Ng N, Swaim LS. Knowledge and attitiudes of pregnant women and their providers towards recommendations for immunization during pregnancy. *Vaccine* 2015; **33**(41): 5445-51.
100. van Lier EAGO, P.J.; Giesbers, H.; van Vliet, J.A.; Hament, J-A.; Drijfhout, I.H.; Zonnenberg-Hoff, I.F.; de Melker, H.E. Vaccination Coverage and Annual Report National Immunisation Programme Netherlands 2020 [in Dutch: Vaccinatiegraad en Jaarverslag Rijksvaccinatieprogramma Nederland 2020], 2021.
101. Omer SB, Salmon DA, Orenstein WA, deHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *N Engl J Med* 2009; **360**(19): 1981-8.
102. Chen RT, Glasser JW, Rhodes PH, et al. Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. The Vaccine Safety Datalink Team. *Pediatrics* 1997; **99**(6): 765-73.
103. Global Vaccine Safety; adverse events following immunization (AEFI). https://www.who.int/vaccine_safety/initiative/detection/AEFI/en/.
104. Fortner KB, Swamy GK, Broder KR, et al. Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women. *Vaccine* 2018; **36**(42): 6354-60.
105. Vygen-Bonnet S, Hellenbrand W, Garbe E, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. *BMC Infect Dis* 2020; **20**(1): 136.
106. Regan AK, Tracey LE, Blyth CC, Richmond PC, Effler PV. A prospective cohort study assessing the reactogenicity of pertussis and influenza vaccines administered during pregnancy. *Vaccine* 2016; **34**(20): 2299-304.
107. Sukumaran L, McCarthy NL, Kharbanda EO, et al. Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes Among Pregnant Women With Prior Tetanus-Containing Immunizations. *JAMA* 2015; **314**(15): 1581-7.
108. Ben Nessib D, Fazaa A, Miladi S, et al. Do immunosuppressive agents hamper the vaccination response in patients with rheumatic diseases? A review of the literature. *Therapie* 2021; **76**(3): 215-9.
109. Keller M, Pittet LF, Zimmermann P. Immunogenicity and safety of routine vaccines in children and adolescents with rheumatic diseases on immunosuppressive treatment - a systematic review. *Eur J Pediatr* 2022; **181**(4): 1329-62.
110. Barug D, Pronk I, van Houten MA, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. *Lancet Infect Dis* 2019; **19**(4): 392-401.
111. Perined. The Dutch Perinatal Registry. www.perined.nl.

PART I

Maternal Tdap vaccination and vaccine-induced antibodies in newborns

CHAPTER 2

Study protocol of the PIMPI-project, a cohort study on acceptance, tolerability and immunogenicity of second trimester maternal pertussis immunization in relation to term and preterm infants

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Abstract

Background

Maternal immunization confers passive immunity to the fetus by transplacental antibody transfer. Infants may be better protected against pertussis if the mother received a diphtheriae, tetanus and acellular pertussis (Tdap) vaccination in the second trimester of pregnancy compared to the third trimester. This study evaluates IgG antibody concentrations in term and preterm infants at birth and two months after birth after maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w of gestation vs third trimester Tdap-vaccination. Further aims are assessing the determinants that underlie acceptance of second trimester maternal Tdap-vaccination as well as the tolerability of vaccination.

Methods

This prospective cohort study consists of two parts. In the acceptance part, pregnant women complete a questionnaire on determinants that underlie acceptance of a second trimester Tdap-vaccination, which is offered subsequently between $20^{0/7}$-$24^{0/7}$w of gestation. Vaccinated women complete an additional questionnaire on vaccination tolerability. Vaccinated women may also participate in the immunogenicity part, in which blood is drawn from mother at delivery and from infant at birth and two months after birth. Women are also eligible for the immunogenicity part if they received a Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w of gestation via the national immunization program and get hospitalized for an imminent preterm delivery. Blood sampling continues until 60 term and 60 preterm mother-infant-pairs have been included. Pertussis-specific IgG antibody concentrations are determined in serum using a fluorescent bead-based multiplex immunoassay. For term infants, non-inferiority in IgG antibody concentrations against pertussis toxin (anti-PT) will be assessed referred to a historical control group in which mothers were Tdap-vaccinated between $30^{0/7}$-$32^{0/7}$w of gestation. For preterm infants, non-inferiority of anti-PT IgG concentrations is referred to as 85% of infants having ≥20 international units/mL at two months after birth.

Discussion

This study investigates acceptance, tolerability and immunogenicity regarding maternal Tdap-immunization between $20^{0/7}$-$24^{0/7}$w of gestation. Its results provide insight into the effects of second trimester Tdap-vaccination on IgG antibody concentrations in term and preterm infants before primary infant vaccinations. Results on acceptance and tolerability guide antenatal care providers in communication with pregnant women and maintain the safety of second trimester Tdap-vaccination.

Background

Pertussis is a respiratory infectious disease caused mainly by *Bordetella pertussis*. Especially young infants are at increased risk of severe complications, hospitalization and sometimes even death.[1] Infant vaccinations against pertussis started around 1950 with steady high coverage, leading to lower incidences.[2,3] However, in the nineties of the previous century, pertussis re-emerged in many countries, including the Netherlands.[4] Incidences in all ages increased with epidemic peaks every 3-4 years (figure 1).[5]

The Netherlands implemented several changes in the national immunization program in response to the increase. In 1999, the first pertussis containing vaccination was scheduled at 2 months (m) instead of 3m. Late in 2001, an acellular pertussis component was added to the preschool diphtheria, tetanus and poliomyelitis booster dose at 4 years (y) of age and from 2005 onwards, the primary infant pertussis vaccinations also contained an acellular pertussis component instead of whole cell pertussis. However, surveillance data show that the incidence in young infants did not decrease following these changes (figure 1).[5] In fact, an increase within this vulnerable age group was observed during every epidemic peak.[2] Adolescents and adults are likely a source of transmission to young infants.[6]

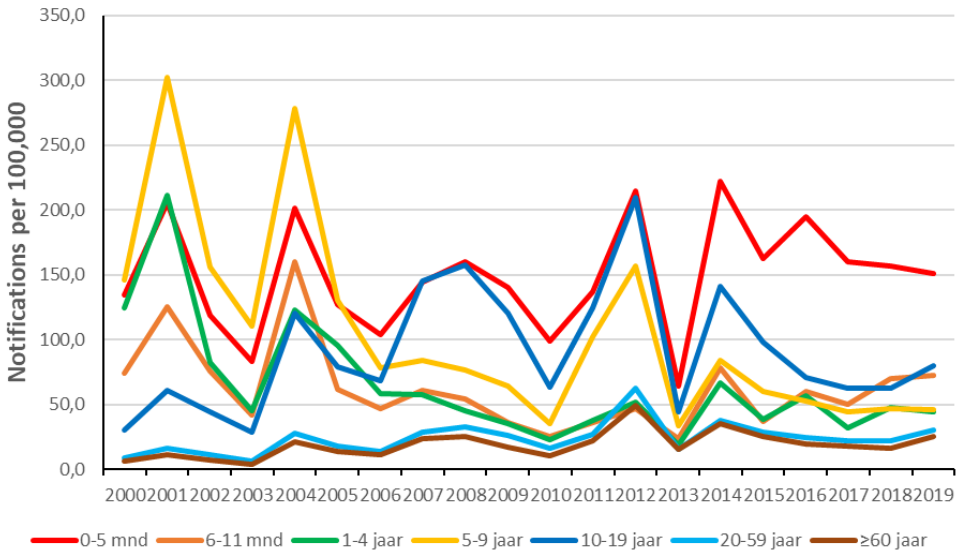

Figure 1. Number of pertussis notifications per 100,000 per age category in 2005-2019.[7]

In 2011, increased incidence rates of reported pertussis cases were followed

by a large outbreak in 2012 in the Netherlands and surrounding countries, including England.[8] In response to an increasing number of pertussis related deaths, the English government decided to offer a maternal pertussis vaccination by means of a tetanus, diphtheria, acellular pertussis and poliomyelitis (Tdap-IPV) vaccine to all pregnant women during the third trimester. Maternal vaccination induces protection of young, not yet (fully) vaccinated infants. It confers passive immunity to the fetus by transplacental antibody transfer, which starts around 17 weeks (w) of gestational age (GA) and peaks in the third trimester.[9] After birth, maternal antibodies wane rapidly over time.[10]

The uptake in England ranged around 70% and observational data showed a high vaccine effectiveness without any important safety concerns.[10,11] To date, over 25 countries recommend maternal pertussis immunization with reassuring effectiveness and safety data. In December 2015, the Health Council of the Netherlands advised to offer a pertussis vaccination to all pregnant women in their third trimester.[12] In July 2018, the Ministry of Health, Welfare and Sports, decided to follow the advice of a maternal pertussis vaccination program. First vaccinations were offered mid December 2019.

Most countries offer third trimester Tdap-vaccination because of its benefits for newborns in general. However, preterm infants are less protected by third trimester Tdap-vaccination due to too short time intervals between vaccination and delivery. This was demonstrated in data from England, showing that preterm infants were overrepresented in pertussis hospitalizations and with an increase from 9.8% to 12.1% in the share of preterm infants after the introduction of third trimester Tdap-vaccination.[13] A similar overrepresentation of preterm infants among pertussis hospitalizations is shown in Norway (10% vs 5.2%),[14] and in the Netherlands (11.8% vs 7.8%).[15] To offer women more opportunities for vaccination, England widened the interval for maternal Tdap-vaccination to the second trimester,[16] resulting in an increase of the vaccination coverage of about 15%.[17] The overrepresentation of pertussis in preterm infants in England reduced strongly since widening this interval.[18] Switzerland also recommends vaccination from second trimester onwards and showed that infants of second trimester vaccinated mothers had higher antibody levels at birth than infants of third trimester vaccinated mothers.[19] Importantly, they also showed that preterm infants of second trimester vaccinated mothers had higher pertussis antibody levels at birth than preterm infants of third trimester vaccinated mothers.[20] By contrast, Winter et al. demonstrated that third trimester Tdap-vaccination was more effective in preventing clinical pertussis than vaccination earlier during pregnancy (85% vs 64%).[21] However, both studies used different endpoints, i.e. Eberhardt et al. used

immunogenicity as outcome measure, while Winter et al. used effectiveness as outcome measure. In the Netherlands, Tdap-vaccines are offered to pregnant women from 22w GA onwards and administered via youth public healthcare services. Studies show that women in their second trimester are less willing to accept the vaccination compared to women later throughout gestation.[22,23] However, these studies were performed without current knowledge that preterm infants are worse off than term infants following third trimester pertussis vaccination.

We set up this study of pregnant women and their infants to fill the knowledge gap on the effects of second trimester maternal Tdap-vaccination for the prevention of pertussis in term and preterm infants. In a prospective study that is divided into two study parts, i.e. acceptance and immunogenicity, we aim to assess the determinants that underlie acceptance of Tdap-vaccination in the second trimester of pregnancy and how second trimester Tdap-vaccination induces maternal antibody levels in term and preterm infants before primary vaccinations. Furthermore, we aim to assess tolerability of a maternal Tdap-vaccination.

Methods/design

Study design and objectives

This study is conducted as a prospective cohort study of pregnant women, with follow-up of their infants up to 2m of age. It is divided into two parts. In the acceptance part, determinants that underlie acceptance of second trimester Tdap-vaccination are assessed using a questionnaire, as followed up by the tolerability after vaccination. In the immunogenicity part, pertussis-specific IgG antibody concentrations are determined in term and preterm infants at birth and 2m after birth if the mother accepted the vaccination between $20^{0/7}$-$24^{0/7}$w GA.

Primary Objectives

Immunogenicity part

- To evaluate non-inferiority of anti-Pertussis Toxin (PT) IgG antibodies in term infants at 2m of age born of mothers who received a Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA, compared to a reference anti-PT IgG at 2m of age in a historical control group of term infants born of mothers who were vaccinated between 30-32w GA in the period January 2014 to February 2016.
- To evaluate non-inferiority of anti-PT IgG in preterm infants at 2m of age born of mothers who received a Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA, as referred to at least 85% of preterm infants having anti-PT IgG

concentrations ≥20 international units (IU)/mL as used in many immunogenicity studies.

Secondary Objectives

Acceptance part

- To assess pregnant women's social cognitive determinants and underlying beliefs on maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA and distinguish results among women who are pregnant for the first time, women who were pregnant before, and in both groups, women with and without a known increased risk of preterm delivery.
- To assess the correlation between social cognitive determinants and underlying beliefs and actual behavior, i.e. acceptance of a maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA.
- To compare social cognitive determinants and underlying beliefs of maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA with those of third trimester maternal vaccination.

Tolerability (extension of the acceptance part)

- To assess tolerability of the maternal Tdap-vaccination, administered to pregnant women between $20^{0/7}$-$24^{0/7}$w GA.
- To assess possible adverse pregnancy outcomes of maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA.

Immunogenicity part

- To compare pertussis specific IgG concentrations at 2m of age (i.e. before the primary infant vaccinations) between term and preterm infants.
- To compare the decay in pertussis-specific maternal IgG concentrations in the first 2m after birth between term and preterm infants.
- To compare pertussis-specific IgG concentrations at delivery between mothers who delivered term and preterm.
- To compare pertussis-specific IgG concentrations in mothers who received second trimester Tdap-vaccination and a group that received third trimester vaccination.
- To determine levels of pertussis-specific IgG transferred from the mother to the neonate relative to the interval from vaccination to delivery, if possible depending on the variation in interval.

Study population and setting

The study population consists of pregnant women who receive primary, secondary or tertiary antenatal care. Participants are included by their antenatal care provider and followed-up prospectively in both the acceptance and immunogenicity study parts. By including women in secondary and tertiary care, we aim to oversample women with an increased risk for preterm delivery, e.g. women with multiple pregnancy, history of preterm delivery, cervical conization in the medical history and uterus anomaly.

In order to be eligible to participate in this study, women must be 18y or older, pregnant, and in relation to the immunogenicity part of the study, both parents (or mother and legal guardian) must be willing to adhere to the protocol and perform all planned visits and sample collections for themselves and their newborn child. Women who meet any of the following criteria are excluded from participation in the immunogenicity part of this study: history of having received a pertussis containing vaccination in the past two years; known or suspected serious underlying condition that can interfere with the results of the study such as but not limited to cancer, autoimmune disease, immunodeficiency, seizure disorder or significant psychiatric illness; receipt of any high-dose (≥20 mg of prednisone daily or equivalent) daily corticosteroids within two weeks of study entry (inhaled or other local steroids are acceptable) with exception of corticosteroids to enhance maturation of fetal lungs in case of imminent early delivery; receipt of other immune modulating medication, for instance biologicals; receipt of blood products or immunoglobulins, within three months of study entry (rhesus negative women who receive anti-rhesus (D) immunoglobulin will not be excluded from the study); presence of bleeding disorder; having experienced a previous severe adverse reaction to any vaccine; receipt of any vaccine(s) within two weeks of study vaccine (except influenza vaccine which may be given concomitantly); all mothers who give birth before $24^{0/7}$w GA.

Recruitment and follow-up

In the acceptance part, women complete an online questionnaire on the determinants of acceptance of second trimester Tdap-vaccination. The vaccine is offered between $20^{0/7}$-$24^{0/7}$w GA and administered by their antenatal care provider if accepted. Vaccinated women complete a second questionnaire on the tolerability of vaccination. They are also eligible for participation in the immunogenicity study part. In this part, a blood sample from the mother and infant (cord blood) is drawn at delivery and a second sample from the infant at 2m of age, i.e. before the first infant vaccination. Study samples are stored at the laboratory of the National

Institute for Public Health and the Environment. Recruitment continues until blood samples are drawn from 60 term and 60 preterm mother-infant-pairs.

During the recruitment phase, two alternative recruitment routes were added to increase inclusion speed for both study parts (figure 2). The alternative acceptance route focuses on recruitment of women for the acceptance part via midwives in primary care facilities. The alternative immunogenicity route focuses on faster recruitment of preterm infants via secondary and tertiary antenatal care.

Alternative acceptance route

After completing the questionnaire on the determinants that underlie acceptance of second trimester Tdap-vaccination, midwifes inform pregnant women about the possibility of getting a Tdap-vaccination via youth public healthcare services. Vaccination status is requested retrospectively via the national immunization registry. The vaccine is not administered by the antenatal care provider in this route.

Alternative immunogenicity route

Antenatal care providers in hospitals ask consent for sampling cord blood and finger-stick-blood if a women gets hospitalized for an imminent preterm delivery and proves that she received a Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA via the national immunization program. In case of an unclear answer, vaccination status is requested retrospectively via the national immunization registry. Further study procedures for blood sampling are identical to those in in the immunogenicity part.

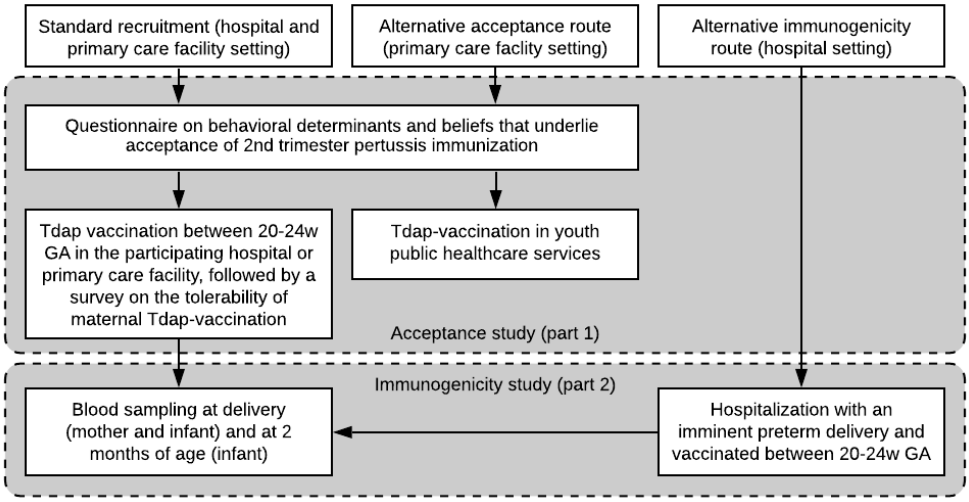

Figure 2. Participant recruitment and alternative recruitment routes in antenatal care in primary care facilities or hospitals.

Questionnaires

Acceptance

The online questionnaire focuses on behavioral determinants and beliefs that underlie acceptance of a second trimester Tdap-vaccination. It consists of about sixty questions and statements assessing demographics, social cognitive determinants, underlying beliefs, past experiences, women's information desires and considerations regarding information provision and implementation of maternal Tdap-vaccination. A Dutch version of the questionnaire is provided in appendix 1.

Tolerability

This questionnaire contains questions about the onset of local reactions and solicited systemic adverse events (AE) within one week post-vaccination. Local reactions include swelling, redness, and pain at the injection site. Systemic AEs include fever, headache, tiredness, nausea, vomiting, diarrhea, dizziness, loss of appetite, stiffness of muscles and joints, itch, abnormal sweating, skin rash, swollen lymph nodes, sore throat, upper airway infection, coughing, fainting, and influenza-like illness. The questionnaire also includes questions about solicited systemic events at baseline, i.e. in the week pre-vaccination. Time interval and duration of symptoms are collected, as well as the use of analgesics, medical intervention, and absence from work and/or other activities. A Dutch version of the survey is provided in appendix 2.

Blood sample collection infant and mother (heel or finger stick)

For IgG testing using the X-map Luminex technology, a maximum of 2mL infant cord blood is used. Furthermore, a maximum of 300 µl blood samples of the mother at birth and of the infants at 2m of age is collected by heel or finger stick. Samples are tested for IgG antibody concentrations against pertussis antigens, diphtheria and tetanus. Antibody concentrations will be assessed in serum using a fluorescent bead-based multiplex immunoassay.[24]

Defining prematurity

We define preterm infants as infants born before 35^{0}w GA, although normally the cut-off for prematurity is set before $37^{0/7}$w GA. We assume that for preterm infants born between $35^{0/7}$-$36^{6/7}$w GA second or third trimester maternal Tdap-vaccination will generally allow enough time for sufficient transfer of antibodies. We will use the same definition for term infants as used in the historical control group, i.e. $\geq 37^{0/7}$w GA.

Investigational product

Boostrix is a suspension for injection in a prefilled syringe containing diphtheria, tetanus and acellular pertussis vaccine (adsorbed, reduced antigen content). The Boostrix vaccine will be given as a single 0.5mL intramuscular injection, in the deltoid muscle of the upper arm between $20^{0/7}$-$24^{0/7}$w GA. For subjects who are ill or have a moderate or high fever (rectal temperature of >38.0 °C), vaccination will be postponed until the symptoms of illness and the fever have disappeared. Pregnant women in the historical cohort[25] received the same vaccine investigational product.

Sample size calculation for immunogenicity part

To reach non-inferiority in term infants, the lower limit of the 95% confidence interval (CI) of the geometric mean concentration (GMC) after second trimester vaccination divided by the GMC after third trimester vaccination must be ≥0.5, with a one-sided 2.5% significance level and 80% power. As the GMC of anti-PT IgG in the historical control group (n=58) was 26.1 IU/mL (95% CI 19.5-35.0), we need to include 53 term infants in the study. Taking into account 10% drop out or failed blood sampling, 58 term infants suffice.

Furthermore, non-inferiority in preterm infants is defined as 85% of infants with an anti-PT IgG above the 20 IU/mL at 2m of age. This cut-off is used in many immunogenicity studies. With 10% precision, we need to include 49 blood samples from preterm mother-infant-pairs. Taking into account 10% drop-out or failed blood sampling, 54 preterm infants suffice. Due to the probability of multiple pregnancies in the preterm infant group and the likeliness of correlation between twins and triplets, preterm mother-infant-pairs are included and counted as one after multiple birth.

Statistical analyses

Acceptance part

Items targeting social cognitive determinants and beliefs are measured on 7-point Likert scales. Items with the same underlying theoretical construct will be averaged into one single construct in case internal consistency is sufficient (Cronbach's alpha $\alpha>.60$ or Pearson correlation coefficient $r>.50$). Spearman's correlation test will be used to explore univariate associations for attitude with social cognitive determinants, underlying beliefs and possible barriers and facilitators. We will control for the false discovery rate in multiple testing according to the Benjamini-Hochberg procedure. Next, variables with the largest predictive

value for women's attitude towards pertussis vaccination during pregnancy will be determined by random forest analysis. We will compare results with a similar study which assessed the determinants of acceptance of third trimester maternal vaccination, to distinguish determinants on the acceptance of maternal Tdap-vaccination in second versus third trimester of pregnancy.[26]

Tolerability (extension of the acceptance part)

The percentage and 95% CI of pregnant women experiencing adverse events (AE) within one week after Tdap-vaccination are described by type and severity of the AE. Using binary generalized mixed models (GLMM), the association between the occurrence of symptoms in the week before and the week after vaccination will be analyzed. Proportions of absence from work and/or other activities, and medical intervention within seven days after vaccination will be calculated together with 95% CI as well as the association of these items before and after vaccination using GLMM.

Immunogenicity part

For term and preterm infants, GMCs and 95% CIs will be calculated for IgG antibodies against three pertussis antigens in the vaccine (PT, filamentous hemagglutinin (FHA), pertactin (Prn)), tetanus and diphtheria in mothers and infants at delivery, and for infants at 2m of age, i.e. before the start of infant vaccination. Differences in GMCs between the two groups will be analyzed with a t-test. All reported p-values are 2-sided, p-values <0.05 are considered significant.

The decay in IgG antibody concentrations against PT, Prn, FHA, tetanus and diphtheria from birth until 2m of age will be analyzed with a paired t-test that compares GMCs at birth and at 2m of age, for term and preterm infants separately. The ratio between maternal GMCs and infant GMCs at birth will be calculated for term and preterm infants separately and stratified for time interval between vaccination and delivery.

For term infants, we will compare the results with another maternal Tdap-vaccination trial in which pregnant women received a Tdap-vaccination between $30^{0/7}$-$32^{0/7}$w GA. Anti-PT IgG concentrations of the 58 term infants from the comparator trial were also measured at 2m of age.

Discussion

General implications of results

This prospective cohort study will investigate the acceptance, tolerability and immunogenicity regarding maternal Tdap-vaccination between $20^{0/7}$ and $24^{0/7}$w GA.

Its results will provide valuable insights into anti-PT IgG antibody concentrations in term and preterm infants before primary infant vaccinations and how the vaccination schedule of these infants may be optimized in response to second trimester Tdap-vaccination. Determinants and beliefs that underlie pregnant women's acceptance of second trimester Tdap-vaccination may guide antenatal care providers in the communication and recommendation of vaccinating early throughout gestation. Furthermore, assessing local reactions and solicited systemic adverse events following second trimester Tdap-vaccination will aid in communication about its safety profile.

Changes in the Dutch vaccination schedule may be considered if non-inferiority of anti-PT IgG antibodies in preterm infants at 2m is addressed. Currently in the Netherlands, a Tdap-vaccination during pregnancy replaces the first infant vaccination for term infants who may then be vaccinated at 3, 5 and 11m with a DTaP-IPV-Hib-HepB vaccine. Preterm infants are excluded from this reduced schedule and receive an extra vaccination at 2m of age. GMCs of preterm infants at 2m of age may inform us whether such a reduced schedule is also feasible for (late) preterm infants if they relate to GMCs at corresponding ages in term infants. For term infants, non-inferiority of anti-PT IgG antibody concentrations after second trimester Tdap-vaccination informs us that anti-PT IgG antibodies may still be higher at 2m of age, compared to third trimester Tdap-vaccination. Since more than 93% of all annual births in the Netherlands are born after $37^{0/7}$w GA,[27] the results of this study may provide reassurance for pregnant women to obtain the maternal Tdap-vaccination at the earliest opportunity throughout gestation, i.e. at 22w GA in the Netherlands.

Strengths

This is the first time that anti-PT IgG concentrations are investigated in term and preterm infants up to 2m of age in response to second trimester Tdap-vaccination. The prospective study design with measurements at birth and 2m of age allows us to assess the velocity of antibody decay before primary infant vaccinations. Drawing blood samples from mother-infant-pairs at delivery provides additional insight in the rate of placental antibody transfer corrected for gestational age. Combining these aspects in immunogenicity with the acceptance part into a single study design results in efficient follow-up of women participating in both study parts and also complete the questionnaire on tolerability.

To our knowledge, behavioral determinants and beliefs that underlie maternal Tdap-vaccination acceptance have not yet been assessed specific for administering the vaccine in the second trimester of pregnancy. The use of multiple

recruitment routes allows us to assess acceptance in women in primary care facilities and hospitals, thus reaching both healthy pregnant women and women with an increased risk of preterm delivery. The results may ultimately be used for communication early in pregnancy, especially when the risk of preterm delivery is addressed.

Limitations

Assessing antibodies in term mother-infant-pairs based on a historical comparator results in performing analyses at different timepoints, which might affect pertussis antibody responses. However, the differences between these cohorts are limited to the time interval of Tdap-vaccination throughout gestation in both studies. Remaining study procedures, e.g. recruitment, data management and the used investigational product, are similar and performed by the same research institute and laboratory.

Since a maternal Tdap-vaccine could be obtained free of charge via study participation, pregnant women with high intention of acceptance may introduce selection bias due to high willingness of participation. After December 2019 when the vaccination is offered within the National Immunization Program for which no money is charged, women may still be likely to participate in this study for obtaining the vaccine from their antenatal care provider, instead of making an appointment for vaccination at a youth public healthcare service. Altogether, the results of second trimester Tdap-acceptance among pregnant women may be estimated more optimistic than in real life.

The results of our study are limited to a follow-up time of 2m after birth. Maternal antibodies are known to interfere with term infants' immune responses after primary vaccination series, which is known as blunting.[25,28-30] The likeliness of a reduced immune response after primary vaccinations is not assessed in infants born of mothers who received second trimester maternal Tdap-vaccination and remains implicated for future research.

Supplementary materials

Appendix 1. Questionnaire on determinants that underlie acceptance of early maternal pertussis immunization (in Dutch)

Vragen	Antwoordmogelijkheden
Persoonlijke informatie	
Op welke datum bent u uitgerekend?	<datum>
Wat zijn de 4 cijfers van uw postcode?	<getal vier cijfers>
Wat is uw leeftijd in jaren?	<getal twee cijfers>
Wat is uw geboorteland?	Nederland, Suriname; (voormalige) Nederlandse Antillen; Turkije; Marokko; anders
Wat is uw hoogst voltooide opleiding?	geen opleiding (lager onderwijs niet afgemaakt); lager onderwijs (basisschool, speciaal basisonderwijs); lager of voorbereidend beroepsonderwijs (zoals LTS, VMBO-basis, kader of GL); middelbaar algemeen voortgezet onderwijs (zoals MAVO, MBO-kort, VMBO-TL); middelbaar beroepsonderwijs (MBO); hoger algemeen en voorbereidend wetenschappelijk onderwijs (zoals HAVO, VWO, atheneum, gymnasium); hoger beroepsonderwijs (HBO); wetenschappelijk onderwijs (universiteit)
Voor de hoeveelste keer bent u zwanger?	1e; 2e; 3e; 4e; 5e; 6e; 7e; 8e; 9e; 10e of vaker
Hoeveel eigen kinderen heeft u?	1; 2; 3; 4; 5; 6; 7; 8; 9; 10 of meer
Wat is de geboortedatum van uw (jongste) kind?[1]	<datum>
Doet uw (jongste) kind mee aan het Rijksvaccinatieprogramma?[1]	ja, volledig (alle vaccinaties gekregen die het voor zijn/haar leeftijd zou moeten hebben); ja, gedeeltelijk (niet alle vaccinaties gekregen die het voor zijn/haar leeftijd zou moeten hebben); nee; weet ik niet
Tijdens mijn zwangerschap sta ik onder controle bij:	verloskundige; klinisch/tweedelijns verloskundige; arts-assistent van het ziekenhuis; gynaecoloog
De onderstaande overtuigingen zijn van toepassing op mij:	

Geloofsovertuiging	1 (helemaal niet van toepassing); 2; 3; 4; 5; 6; 7 (heel erg van toepassing)
Homeopathie	1 (helemaal niet van toepassing); 2; 3; 4; 5; 6; 7 (heel erg van toepassing)
Natuurgeneeswijzen	1 (helemaal niet van toepassing); 2; 3; 4; 5; 6; 7 (heel erg van toepassing)
Antroposofie	1 (helemaal niet van toepassing); 2; 3; 4; 5; 6; 7 (heel erg van toepassing)
Kinkhoest en kinkhoestvaccinatie tijdens de zwangerschap	
Hoe ernstig zijn de gevolgen van kinkhoest voor baby's volgens u?	1 (niet ernstig); 2; 3; 4; 5; 6; 7 (zeer ernstig)
Stel dat u zich niet tijdens de zwangerschap tegen kinkhoest laat vaccineren, hoe groot acht u dan de kans dat uw baby kinkhoest krijgt?	1 (zeer klein); 2; 3; 4; 5; 6; 7 (zeer groot)
Stel dat u zich tijdens de zwangerschap tegen kinkhoest laat vaccineren, hoe groot acht u dan de kans op negatieve gevolgen voor het verloop van uw zwangerschap?	1 (zeer klein); 2; 3; 4; 5; 6; 7 (zeer groot)
Stel dat u zich tijdens de zwangerschap tegen kinkhoest laat vaccineren, hoe groot acht u dan de kans dat uw baby later last krijgt van bijwerkingen?	1 (zeer klein); 2; 3; 4; 5; 6; 7 (zeer groot)
Stel dat u zich tijdens de zwangerschap tegen kinkhoest laat vaccineren, hoe groot acht u dan de kans dat u bijwerkingen krijgt?	1 (zeer klein); 2; 3; 4; 5; 6; 7 (zeer groot)
Hoe ernstig zijn de bijwerkingen van de kinkhoestvaccinatie tijdens de zwangerschap voor uzelf volgens u?	1 (niet ernstig); 2; 3; 4; 5; 6; 7 (zeer ernstig)
Hoe ernstig zijn de bijwerkingen van de kinkhoestvaccinatie tijdens de zwangerschap voor uw baby volgens u?	1 (niet ernstig); 2; 3; 4; 5; 6; 7 (zeer ernstig)
Ik vind dat het doormaken van kinkhoest bijdraagt aan een positieve mentale en lichamelijke ontwikkeling van mijn baby.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat het doormaken van kinkhoest positief is voor mijn baby.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat de kinkhoestvaccinatie tijdens de zwangerschap een goede manier is om negatieve gevolgen van kinkhoest bij baby's te voorkomen.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)

Ik denk dat de kinkhoestvaccinatie tijdens de zwangerschap veilig is voor de zwangere vrouw.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat de kinkhoestvaccinatie tijdens de zwangerschap veilig is voor de baby.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat het kinkhoestvaccin nog onvoldoende op veiligheid is getest bij zwangere vrouwen.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat vaccinaties onvoldoende beschermen tegen de infectieziekten waartegen gevaccineerd wordt.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat er stoffen in vaccins zitten die schadelijk kunnen zijn voor de gezondheid van mijn baby.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat de kinkhoestvaccinatie aan zwangere vrouwen wordt aangeboden zodat de farmaceutische industrie hier geld aan kan verdienen.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat als de kinkhoestvaccinatie al in andere landen (bijv. Engeland en België) aan zwangere vrouwen wordt aangeboden, dat de vaccinatie dan veilig zal zijn.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat vaccineren tegen kinkhoest tijdens de zwangerschap zorgt voor minder kinkhoest bij baby's	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat door het vaccineren tegen kinkhoest tijdens de zwangerschap, baby's beschermd zijn totdat ze zelf gevaccineerd kunnen worden.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat vaccineren tegen kinkhoest tijdens de zwangerschap zorgt voor meer complicaties tijdens mijn zwangerschap.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat vaccineren tegen kinkhoest tijdens de zwangerschap zorgt voor een minder goede weerstand van mijn baby.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat er een goed alternatief is voor kinkhoestvaccinatie tijdens de zwangerschap.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Keuze wel of niet te laten vaccineren tijdens de zwangerschap	
Ik vind het advies van de verloskundige of gynaecoloog om mij te laten vaccineren	1 (helemaal niet belangrijk); 2; 3; 4; 5; 6; 7 (heel erg belangrijk)

tegen kinkhoest tijdens mijn zwangerschap	
Ik vind het advies van mijn partner om mij te laten vaccineren tegen kinkhoest tijdens mijn zwangerschap	1 (helemaal niet belangrijk); 2; 3; 4; 5; 6; 7 (heel erg belangrijk)
Ik denk dat de mensen die belangrijk voor mij zijn het zullen waarderen als ik mij tijdens de zwangerschap tegen kinkhoest laat vaccineren.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat mijn verloskundige of gynaecoloog vindt dat ik mij tijdens de zwangerschap tegen kinkhoest moet laten vaccineren.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik denk dat de meeste zwangere vrouwen zich tijdens de zwangerschap tegen kinkhoest laten vaccineren.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat het bij mijn verantwoordelijkheid als zwangere hoort om mij tijdens de zwangerschap tegen kinkhoest te laten vaccineren om mijn baby te beschermen.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat het bij mijn verantwoordelijkheid als zwangere hoort om de kinkhoestvaccinatie tijdens mijn zwangerschap te weigeren.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat het bij de verantwoordelijkheid van iedere zwangere hoort om zich tijdens de zwangerschap tegen kinkhoest te laten vaccineren om hun baby te beschermen.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat het bij de verantwoordelijkheid van iedere zwangere hoort om de kinkhoestvaccinatie tijdens hun zwangerschap te weigeren.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Stel dat u zich tijdens de zwangerschap niet tegen kinkhoest laat vaccineren en uw baby krijgt later kinkhoest. Hoeveel spijt zult u dan hebben van uw besluit zich niet te laten vaccineren?	1 (helemaal geen spijt); 2; 3; 4; 5; 6; 7 (heel erg veel spijt)
Stel dat u zich tijdens de zwangerschap wel tegen kinkhoest laat vaccineren en uw baby krijgt last van bijwerkingen. Hoeveel spijt zult u dan hebben van uw besluit zich te laten vaccineren?	1 (helemaal geen spijt); 2; 3; 4; 5; 6; 7 (heel erg veel spijt)

Mij laten vaccineren tegen kinkhoest tijdens de zwangerschap is iets waar ik lang over na moet denken.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik ben mij bewust van de voor- en nadelen van het vaccineren tegen kinkhoest tijdens mijn zwangerschap.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik heb getwijfeld over het wel of niet laten vaccineren tegen kinkhoest tijdens mijn zwangerschap.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Keuze wel of niet te vaccineren tijdens de zwangerschap (vervolg)	
Als ik eraan denk om mij tijdens mijn zwangerschap te laten vaccineren, dan vind ik dat:	1 (helemaal niet eng); 2; 3; 4; 5; 6; 7 (heel erg eng)
Wat vindt u eng als u aan vaccineren tijdens de zwangerschap denkt?[2]	<open invulveld>
Als ik eraan denk dat mijn pasgeboren baby kinkhoest zou kunnen krijgen, dan vind ik dat:	1 (helemaal niet eng); 2; 3; 4; 5; 6; 7 (heel erg eng)
Wat vindt u eng als u eraan denkt dat uw baby kinkhoest zou kunnen krijgen?[3]	<open invulveld>
Als er een alternatief is voor het vaccineren tegen kinkhoest tijdens de zwangerschap, dan zal ik daarvoor kiezen.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat ongeboren baby's te kwetsbaar zijn om ze al tijdens de zwangerschap te belasten met een vaccin.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind dat vaccineren tijdens de zwangerschap tegenstrijdig is met zo min mogelijk medicijngebruik tijdens de zwangerschap.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind het vaccineren tegen kinkhoest tijdens mijn zwangerschap:	1 (heel erg slecht); 2; 3; 4; 5; 6; 7 (heel erg goed)
Ik vind het vaccineren tegen kinkhoest tijdens mijn zwangerschap:	1 (heel erg onbelangrijk); 2; 3; 4; 5; 6; 7 (heel erg belangrijk)
Ik vind het vaccineren tegen kinkhoest tijdens mijn zwangerschap:	1 (heel erg onnodig); 2; 3; 4; 5; 6; 7 (heel erg nodig)
Ik ben van plan mij tijdens mijn zwangerschap tegen kinkhoest te laten vaccineren.	1 (zeker niet); 2; 3; 4; 5; 6; 7 (zeker wel)

Ik verwacht dat ik mij tijdens mijn zwangerschap tegen kinkhoest zal laten vaccineren.	1 (zeker niet); 2; 3; 4; 5; 6; 7 (zeker wel)
Het is waarschijnlijk dat ik mij tijdens mijn zwangerschap tegen kinkhoest zal laten vaccineren.	1 (zeker niet); 2; 3; 4; 5; 6; 7 (zeker wel)
Informatiebehoefte en praktische overwegingen	
Hoeveel vertrouwen heeft u in de informatie die u van uw verloskundige of gynaecoloog krijgt over de kinkhoestvaccinatie tijdens de zwangerschap?	1 (helemaal geen vertrouwen); 2; 3; 4; 5; 6; 7 (heel veel vertrouwen)
Hoeveel vertrouwen heeft u in informatie van het RIVM over de kinkhoestvaccinatie tijdens de zwangerschap?	1 (helemaal geen vertrouwen); 2; 3; 4; 5; 6; 7 (heel veel vertrouwen)
Hoeveel vertrouwen heeft u in het besluit van de overheid om een kinkhoestvaccinatie tijdens de zwangerschap aan te bieden?	1 (helemaal geen vertrouwen); 2; 3; 4; 5; 6; 7 (heel veel vertrouwen)
Ik vind het niet fijn dat de kinkhoestvaccinatie een combinatievaccin is, waardoor ik ook gevaccineerd word tegen andere infecties (difterie en tetanus).	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik vind het fijn als mijn kind iets later kan beginnen met de vaccinaties en een prik minder nodig heeft, doordat ik me tijdens de zwangerschap laat vaccineren.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Ik voel mij door anderen onder druk gezet bij het maken van een keuze rondom het vaccineren tegen kinkhoest tijdens mijn zwangerschap.	1 (helemaal mee oneens); 2; 3; 4; 5; 6; 7 (helemaal mee eens)
Dit waren alle vragen. Als u nog opmerkingen heeft over de vragenlijst, dan kunt u dat hier aangeven.	<open invulveld>

[1]Vraag van toepassing als *'Hoeveel eigen kinderen heeft u?'* is 1 of meer. 2Vraag van toepassing als *'Als ik eraan denk om mij tijdens mijn zwangerschap te laten vaccineren, dan vind ik dat:'* is 4 of hoger. [3]Vraag van toepassing als *'Als ik eraan denk dat mijn pasgeboren baby kinkhoest zou kunnen krijgen, dan vind ik dat:'* is 4 of hoger.

Appendix 2. Questionnaire on local reactions and solicited systemic adverse events before and after vaccination (in Dutch)

Vragen	**Antwoordmogelijkheden**
Persoonsgegevens	
Op welke datum kreeg u de kinkhoestvaccinatie?	<datum>
Heeft u een chronische ziekte/aandoening?	ja; nee
Welke?	<open invulveld>
Gebruikt u hiervoor medicijnen?	ja; nee
Welke medicijnen?	<open invulveld>
Heeft u een aandoening die invloed kan hebben op uw zwangerschap?	ja; nee
Welke?	<open invulveld>
Symptomen in de week vóór de vaccinatie Geef hieronder aan of u symptomen had in de week vóórafgaande aan de vaccinatie. Als u bij de symptomen 'ja' invult, beantwoord dan ook de vervolgvragen.	
Had u last van koorts?	ja; nee
Wat was de hoogst gemeten temperatuur?	38 tot 39°C; 39 tot 40°C; 40 tot 41°C; hoger dan 41°C
Hoe is dit gemeten?	rectaal; oksel; oor; tast; anders; niet gemeten
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van hoofdpijn?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van vermoeidheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van misselijkheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van braken?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7

Toelichting	<open invulveld>
Had u last van harde buiken?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van diarree?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van duizeligheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van een verminderde eetlust?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van gewrichts- of spierstijfheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van jeuk?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van overmatig zweten?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van huiduitslag?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van gezwollen klieren in de nek, oksel of lies?	ja; nee

Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van keelpijn?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van verkoudheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van hoesten?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van flauwvallen?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van griep of griepachtige klachten?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van iets anders? Zo ja, vul in:	<open invulveld>
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>

Vragen over de symptomen vóór de vaccinatie

Als u op alle vragen over de symptomen 'nee' heeft ingevuld, dan kunt u de volgende vragen overslaan.

Heeft u medische hulp gezocht naar aanleiding van de symptomen?	ja; nee
Hoe heeft u medische hulp gezocht?	telefoon huisarts; bezoek huisarts; bezoek ziekenhuis; opname in ziekenhuis;

	natuurgeneeskundige; extra contact met verloskundige of gynaecoloog; anders
Heeft u pijnstillers of medicijnen gebruikt in de week voor de vaccinatie?	ja; nee
Welke pijnstillers?	<open invulveld>
Hoe lang heeft u de pijnstillers gebruikt in de week voor de vaccinatie?	1 tot 2 dagen; 3 of meer dagen
Heeft u zich vanwege de symptomen ziek gemeld voor uw werk, in de week voor de vaccinatie?	ja; nee
Hoe lang heeft u zich vanwege de klachten ziekgemeld van uw werk?	1 tot 2 dagen; 3 of meer dagen
Vul in als er nog bijzonderheden waren in de week voor de vaccinatie:	<open invulveld>
Symptomen in de week ná de vaccinatie	
Geef hieronder aan of u symptomen had in de week ná de vaccinatie. Als u bij de symptomen 'ja' invult, beantwoord dan ook de vervolgvragen.	
Had u last van koorts?	ja; nee
Wat was de hoogst gemeten temperatuur?	38 tot 39°C; 39 tot 40°C; 40 tot 41°C; hoger dan 41°C
Hoe is dit gemeten?	rectaal; oksel; oor; tast; anders; niet gemeten
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van hoofdpijn?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van vermoeidheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van misselijkheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van braken?	ja; nee
Hoe ernstig was het?	iets; matig; veel

Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van harde buiken?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van diarree?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van duizeligheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van een verminderde eetlust?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van gewrichts- of spierstijfheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van jeuk?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van overmatig zweten?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van huiduitslag?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>

Had u last van gezwollen klieren in de nek, oksel of lies?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van keelpijn?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van verkoudheid?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van hoesten?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van flauwvallen?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van griep of griepachtige klachten?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Heeft u last gehad van pijn op de prikplek?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Heeft u last gehad van roodheid op de prikplek?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Heeft u last gehad van zwelling op de prikplek?	ja; nee
Hoe ernstig was het?	iets; matig; veel

Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Heeft u last gehad van een harde bult op de prikplek?	ja; nee
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Had u last van iets anders? Zo ja, vul in:	<open invulveld>
Hoe ernstig was het?	iets; matig; veel
Wanneer is dit begonnen?	<datum>
Hoeveel dagen heeft het geduurd?	1; 2; 3; 4; 5; 6; 7; meer dan 7
Toelichting	<open invulveld>
Vragen over de symptomen ná de vaccinatie	
Als u op alle vragen over de symptomen 'nee' heeft ingevuld, dan kunt u de volgende vragen overslaan.	
Heeft u medische hulp gezocht naar aanleiding van de symptomen?	ja; nee
Hoe heeft u medische hulp gezocht?	telefoon huisarts; bezoek huisarts; bezoek ziekenhuis; opname in ziekenhuis; natuurgeneeskundige; extra contact met verloskundige of gynaecoloog; anders
Heeft u pijnstillers of medicijnen gebruikt in de week na de vaccinatie?	ja; nee
Welke pijnstillers?	<open invulveld>
Op welk moment heeft u de pijnstillers genomen?	0-6 uur na de vaccinatie; 4-24 uur na de vaccinatie; 24-48 uur na de vaccinatie; langer dan 48 uur na de vaccinatie
Hoe lang heeft u de pijnstillers gebruikt in de week na de vaccinatie?	1 tot 2 dagen; 3 of meer dagen
Heeft u zich vanwege de symptomen ziek gemeld voor uw werk, in de na voor de vaccinatie?	ja; nee
Hoe lang heeft u zich vanwege de klachten ziekgemeld van uw werk?	1 tot 2 dagen; 3 of meer dagen
Vul in als er nog bijzonderheden waren in de week na de vaccinatie:	<open invulveld>

References

1. Vegelin AL, van Vught AJ, Wolfs TF, Kimpen JL, Geelen SP. [Pertussis in young infants]. *Ned Tijdschr Geneeskd* 1998; **142**(49): 2657-60.
2. Schurink-van 't Klooster TM. the National Immunisation Programme in the Netherlands; surveillance and developments in 2015-2016. Bilthoven: National Institute for Public Health and the Environment, 2016.
3. van Wijhe M, McDonald SA, de Melker HE, Postma MJ, Wallinga J. Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis. *Lancet Infect Dis* 2016.
4. de Melker HE, Schellekens JFP, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MAE. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. *Emerg Infect Dis* 2000; **6**(4): 348-57.
5. van der Maas NAT, Mooi FR, de Greeff SC, Berbers GAM, Conyn-Spaendonck MAE, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? *Vaccine* 2013; **31**(41): 4541-7.
6. de Greeff SC, Mooi FR, Westerhof A, et al. Pertussis disease burden in the household: how to protect young infants. *Clin Infect Dis* 2010; **50**(10): 1339-45.
7. Schurink-van 't Klooster TM, de Melker HE. The National Immunisation Programme in the Netherlands - Surveillance en Developments in 2019-2020, 2020.
8. whooping cough vaccination; coverage may be widened. *Br Med J (Clin Res Ed)* 2012; **345**(7868): E5201.
9. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; **36**(5): 248-55.
10. Amirthalingam G, Campbell H, Ribeiro S, et al. sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. *CID* 2016.
11. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ* 2014; **349**: g4219.
12. Gezondheidsraad. Vaccinatie tegen kinkhoest: doel en strategie. Den Haag: Gezondheidsraad, 2015.
13. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. *Arch Dis Child* 2017.
14. Riise OR, Laake I, Vestrheim D, et al. Risk of Pertussis in Relation to Degree of Prematurity in Children Less Than 2 Years of Age. *Pediatr Infect Dis J* 2017; **36**(5): e151-e6.
15. van der Maas NAT, Sanders EAM, Versteegh FGA, Baauw A, Westerhof A, de Melker HE. Pertussis hospitalizations among term and preterm infants: clinical course and vaccine effectiveness. *BMC Infect Dis* 2019; **19**(1): 919.
16. Amirthalingam G, Brown CS, Campbell H, Chand MA, Fry NK. New Public Health England guidelines for managing pertussis in England. *J Infect* 2017; **74**(2): 202-4.
17. Pertussis vaccination programme for pregnant women update: vaccine coverage in England, April to June 2018: Public Health England, 2018.
18. Tessier E, Campbell H, Ribeiro S, et al. Impact of extending the timing of maternal pertussis vaccination on hospitalized infant pertussis in England, 2014 - 2018. *Clin Infect Dis* 2020.
19. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. *Clin Infect Dis* 2016.
20. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization. *Clin Infect Dis* 2017; **64**(8): 1129-32.
21. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. *Clin Infect Dis* 2017; **64**(1): 3-8.
22. van Lier A, Steens A, Ferreira JA, van der Maas NA, de Melker HE. Acceptance of vaccination during pregnancy: experience with 2009 influenza A (H1N1) in the Netherlands. *Vaccine* 2012; **30**(18): 2892-9.

23. Healy CM, Rench MA, Montesinos DP, Ng N, Swaim LS. Knowledge and attitiudes of pregnant women and their providers towards recommendations for immunization during pregnancy. *Vaccine* 2015; **33**(41): 5445-51.
24. van Gageldonk PG, van Schaijk FG, van der Klis FR, Berbers GA. Development and validation of a multiplex immunoassay for the simultaneous determination of serum antibodies to Bordetella pertussis, diphtheria and tetanus. *J Immunol Methods* 2008; **335**(1-2): 79-89.
25. Barug D, Pronk I, van Houten MA, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. *Lancet Infect Dis* 2019; **19**(4): 392-401.
26. Anraad C, Lehmann BA, Visser O, et al. Social-psychological determinants of maternal pertussis vaccination acceptance during pregnancy among women in the Netherlands. *Vaccine* 2020; **38**(40): 6254-66.
27. Peristat. 2021. https://www.peristat.nl/.
28. Ladhani SN, Andrews NJ, Southern J, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. *Clin Infect Dis* 2015; **61**(11): 1637-44.
29. Hardy-Fairbanks AJ, Pan SJ, Decker MD, et al. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. *Pediatr Infect Dis J* 2013; **32**(11): 1257-60.
30. Abu Raya B, Edwards KM, Scheifele DW, Halperin SA. Pertussis and influenza immunisation during pregnancy: a landscape review. *Lancet Infect Dis* 2017; **17**(7): e209-e22.

CHAPTER 3

Maternal pertussis immunization and immunoglobulin G levels in early- to late-term and preterm infants

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Abstract

Importance

Maternal tetanus, diphtheria, and acellular pertussis (Tdap) vaccination protects newborns against severe pertussis. Data on transplacental antibody transfer on Tdap vaccination before 24 weeks' gestation remain scarce and are particularly relevant for preterm infants to increase the time interval for maternal antibody transfer.

Objective

To assess noninferiority of anti–pertussis toxin (anti-PT) immunoglobulin G (IgG) antibody levels at age 2 months in early- to late-term infants following Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation compared with $30^{0/7}$ and $33^{0/7}$ weeks' gestation and compared with preterm infants.

Design, Setting and Participants

This prospective, multicenter cohort study included pregnant women aged 18 years or older in birthing centers and hospitals in the Netherlands between August 2019 and November 2021 who received Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation. Women with imminent premature birth were recruited if they had received maternal Tdap vaccination between 20 and 24 weeks' gestation. Blood samples were collected from mothers at delivery, from the umbilical cord, and from infants at age 2 months. Data from infants' blood samples at age 2 months were compared with a reference cohort (recruited between January 2014 and February 2016) of early- to late-term infants of the same age whose mothers had received Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation.

Exposure

Maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation or $30^{0/7}$ and $33^{0/7}$ weeks' gestation.

Main outcomes and measures

The primary outcome was the geometric mean concentration (GMC) of anti-PT IgG antibodies in early- to late-term infants ($\geq 37^{0/7}$ weeks' gestation) at age 2 months, comparing maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' vs $30^{0/7}$ and $33^{0/7}$ weeks' gestation (reference cohort). Anti-PT GMC in 2-month-old infants born preterm ($<35^{0/7}$ weeks' gestation) compared with early- to late-term infants after maternal Tdap vaccination between 20 and 24 weeks' gestation was a secondary outcome.

Results

In total, 221 women who delivered 239 offspring were enrolled in the study; 66 early- to late-term infants (median gestational age [GA], 40.6 weeks [IQR, 39.8-41.0 weeks]; 38 [57.6%] male) and 73 preterm infants (median GA, 32.1 weeks [IQR, 29.5-33.0 weeks]; 42 [54.5%] female) had blood samples collected at 2 months of age. Anti-PT GMC was 14.7 IU/mL (95% CI, 10.6-20.4 IU/mL) in early- to late-term infants following maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation compared with 27.3 IU/mL (95% CI, 20.1-37.1 IU/mL) in 55 infants in the reference group (median GA, 40.3 [IQR, 39.1-41.0]; 33 [60.0%] female). The mean anti-PT GMC in preterm infants in the study group was 11.2 IU/mL (95% CI, 8.1-15.3 IU/mL) (P = .23 compared with early- to late-term infants).

Conclusion and Relevance

In this cohort study, 2-month-old preterm and early- to late-term infants showed significantly lower anti-PT antibody levels following maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation compared with $30^{0/7}$ and $33^{0/7}$ weeks' gestation; preterm and early- to late-term infants had similar anti-PT antibody levels, but both groups showed significantly lower antibody levels compared with the reference group. Epidemiological research should investigate whether maternal Tdap vaccination before 24 weeks' gestation provides sufficient protection against clinical pertussis, particularly in preterm infants, as long as no correlate of protection is available.

Introduction

According to the World Health Organization (WHO), 81% of infants worldwide (105 million) received 3 doses of a diphtheria, tetanus, and pertussis vaccine in 2021, protecting them against vaccine-preventable diseases that may cause serious, even fatal, illness and disability.[1] Despite high vaccine coverage, pertussis remains endemic in many countries. Newborns and infants too young to be fully vaccinated are at the highest risk of severe complications.[2] To protect newborns and infants in the first months of life, maternal vaccination with a tetanus, diphtheria, and acellular pertussis (Tdap) vaccine from 20 weeks' gestation onward has been offered to all pregnant women in the Netherlands since December 2019. Infant diphtheria, tetanus, and pertussis (DTaP), inactivated poliovirus (IPV), Haemophilus influenzae type b, and hepatitis B vaccinations are given at 3, 5, and 11 months of age (2 + 1 dose schedule) for protection against pertussis provided that the mother received Tdap vaccination during pregnancy. An extra vaccination at 2 months of age (3 + 1 dose schedule) after maternal Tdap vaccination is advised if an infant is born before 37 weeks' gestation or if the time interval between maternal vaccination and delivery is shorter than 2 weeks, since transfer of immunity against pertussis on maternal Tdap vaccination may be insufficient.

During pregnancy, maternal immunoglobulin G (IgG) antibodies are actively transferred across the placenta, mediated by the neonatal Fc receptor expressed on syncytiotrophoblast cells. This saturable process initiates at approximately 13 to 17 weeks' gestation and increases throughout gestation. Around 33 to 36 weeks' gestation, fetal IgG antibody levels exceed maternal IgG serum levels and increase to 150% of maternal levels near the due delivery date.[3] Tdap vaccination in the third trimester enhances maternal antipertussis IgG antibody levels in newborns.[4-7] Maternal Tdap vaccination was reported to prevent 70% to 90% of clinically confirmed pertussis cases and about 90.5% of pertussis hospitalizations in newborns and infants younger than 3 months of age in the UK from 2013 to 2018.[8,9]

There is no consensus on the optimal timing of maternal Tdap vaccination to achieve the highest antibody transfer. Most studies suggest that Tdap vaccination early in the third trimester results in the highest anti–pertussis toxin (anti-PT) IgG antibody levels at birth,[4-7] while a Swiss study favored second-trimester vaccination, potentially due to a longer time interval between Tdap vaccination and delivery.[10,11] Recently, it was estimated that a period of 7.5 weeks or more before delivery optimizes antibody transfer.[5] Tdap vaccination before 24 weeks' gestation may therefore be particularly relevant for preterm offspring, the group most vulnerable for severe pertussis. Preterm infants have a hospitalization rate for

pertussis that is 1.5-times higher than predicted based on the total proportion of infants in the national UK birth cohort.[12] Offering maternal Tdap vaccination from 20 weeks' gestation also widens the opportunity for pregnant women to receive the vaccine, but few studies have reported antibody levels after maternal Tdap vaccination at or before 24 weeks' gestation or in preterm infants.[6,11] These studies had insufficient power to draw firm conclusions.

In this study, pertussis-specific IgG antibody levels after maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation were evaluated in early- to late-term (hereafter, term) and preterm offspring with follow-up until 2 months of age. We primarily assessed whether maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation would be associated with similar anti-PT antibody levels in term infants at 2 months of age compared with maternal Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation. Therefore, data were compared with those from a reference study (recruitment between January 2014 and February 2016) including 55 term infants following maternal Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation.[13] Additionally, we compared antibody levels in term and preterm infants following maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation.

Methods

Study participants

In this prospective, multicenter cohort study, antenatal care practitioners working in birthing centers or hospitals recruited pregnant women aged 18 years or older between August 2019 and November 2021. The study design and procedures were previously described.[14] In brief, women were included through 2 recruitment routes; from August 2019, healthy pregnant women were invited to participate and received Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation as part of the study. In addition, after 2019, once the Dutch National Immunisation Programme (NIP) offered Tdap vaccination to all pregnant women from 20 weeks' gestation onward, women with imminent preterm labor were recruited on presentation at the hospital provided that they received Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation. These women were vaccinated through the NIP, unrelated to this study but with the same Tdap vaccine as used in the study. Women were excluded if they had received Tdap vaccination within the past 2 years or if there was a known or suspected underlying condition that could interfere with study results. Other exclusion criteria were previously described.[14] Mother-infant pairs were followed up until 2 months after delivery. Data on *Bordetella pertussis*–specific IgG antibodies from mother-infant pairs in the study were compared with data from the reference study performed between

January 2014 and February 2016 that comprised term infants at age 2 months after maternal Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation.[13] Both studies used identical vaccines and study procedures for collection and timing of collection of blood samples. Laboratory procedures were performed in the same laboratory using identical procedures. This study was conducted in accordance with the Declaration of Helsinki and approved by the Central Committee on Research Involving Human Subjects in the Netherlands. Oral and written informed consent was obtained from parents or legal guardians. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Maternal vaccine

Pregnant women received a Tdap vaccine (Boostrix) containing adsorbed *B. pertussis* antigens (ie, inactivated PT, filamentous hemagglutinin [FHA], pertactin [Prn], diphtheria toxoid [DT], and tetanus toxoid [TT]).[15] The Tdap vaccine was administered as a single 0.5-mL intramuscular injection in the deltoid muscle.

Blood sampling

Finger-stick blood samples (≤300 μL) were collected from mothers within 24 hours after delivery. Umbilical cord blood samples (≤2 mL) were collected at delivery, and heel-stick blood samples from infants (≤300 μL) were collected during home visits before primary vaccination at age 2 months (±5 days). For preterm infants, who often start receiving vaccinations between 6 and 9 weeks in the Netherlands, blood samples were collected before the first vaccination. Serum samples were stored at −20 °C awaiting analyses.

Laboratory analyses

Immunoglobulin G antibody concentrations against PT, FHA, Prn, DT, and TT were measured by bead-based fluorescent multiplex immunoassay using Luminex xMAP technology (ThermoFisher Scientific), as previously described.[16] For the *B. pertussis* antigens, the assay was calibrated against the WHO international standard for pertussis antiserum (serum reference 06/140), interpolated using a 5-parameter fit, and expressed in international units (IU/mL).

Statistical analyses

Anti-PT IgG antibody levels following maternal Tdap vaccination are associated with prevention of clinical pertussis.[17] Our primary outcome was to assess noninferiority of anti-PT antibody levels in term infants at 2 months of age following

maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation compared with Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation (reference cohort). The lower limit of the 95% CI of the geometric mean concentration ratio (GMR) between the main and the reference cohorts was set at 0.5 or greater for noninferiority. Secondary outcomes were the geometric mean concentration (GMC) of PT IgG levels in preterm infants at 2 months' postnatal age after maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation compared with the term cohort after maternal Tdap vaccination between 20 and 24 weeks' gestation and the IgG antibody levels against all Tdap vaccine antigens (ie, PT, FHA, Prn, DT, and TT) in blood samples from infants at 2 months of age, the umbilical cord, and mothers at delivery among term and preterm mother-infant pairs (eFigure in Supplement 1).

To assess our primary research question and allow 80% power and an α of 5%, 58 term and 54 preterm mother-infant pairs were required.[14] We aimed for inclusion of 60 pairs in each group to allow loss to follow-up regarding the available blood samples.

For the scope of this study, we defined preterm as birth between $24^{0/7}$ and $34^{6/7}$ weeks' gestation since offspring antibody levels are expected to exceed maternal antibody levels at the end of this time window, and these late-preterm offspring may therefore resemble offspring born at full term regarding transplacental antibody transfer.[3] Term birth was defined as $37^{0/7}$ or more weeks' gestation.

Comparison of baseline characteristics was done using either t, Mann-Whitney U, or Fisher exact test. The IgG-antibody concentrations against all antigens were log-transformed and computed into GMCs with corresponding 95% CIs. In all groups, including the reference cohort,[13] GMCs at different time points were assessed using generalized estimating equation models with a gaussian distribution with identity link function. An exchangeable correlation structure enabled adjustment for similarities in antibody levels among siblings who were twins or triplets. No additional adjustment was applied. The GMRs were calculated from the GMCs within different groups and expressed with 95% CIs. R, version 2023.03.1 (R Project for Statistical Computing) was used with the geepack package for analyses.[18] Findings were based on available data, and missing data were handled by complete participant analyses. Two-sided $P < .05$ was considered significant.

Results

In total, 221 pregnant women who received second-trimester Tdap vaccination were included. They delivered 239 offspring, of whom 148 (61.9%) were term and

91 (38.1%) were preterm. The preterm offspring included 14 pairs of twins and 2 sets of triplets. All 148 term offspring (range, $37^{0/7}$-$42^{0/7}$ weeks' gestation) were singletons; 66 of these (28 [42.4%] female; 38 [57.6%] male) had a blood sample collected at 2 months of age. The 91 preterm offspring (range, $25^{2/7}$-$34^{6/7}$ weeks' gestation) were born to 73 mothers, and 73 of these offspring (42 [54.5%] female; 35 [45.5%] male) had a blood sample obtained at age 2 months (Figure 1). Detailed demographics of study and reference mother-infant pairs are shown in Table 1. The median gestational age (GA) at birth was not significantly different between term infants in the study group (40.6 weeks [IQR, 39.8-41.0 weeks]) and the reference group of 55 infants (33 [60.0%] female; 22 [40.0%] male; median GA, 40.3 weeks [IQR, 39.1-41.0 weeks]). Median GA was significantly different for preterm offspring (32.1 weeks [IQR, 29.5-33.0 weeks]) compared with term offspring in both the study cohort and the reference cohort. The media GA at maternal Tdap vaccination in the study groups of term and preterm mother-infant pairs (22.0 weeks [IQR, 20.9-23.1 weeks] and 22.9 weeks [IQR, 22.0-23.4 weeks], respectively) was significantly different from the median GA in the term mother-infant pairs in the reference cohort (31.1 weeks [IQR, 30.5-31.7 weeks]). The median time interval between maternal Tdap vaccination and delivery was 18.3 weeks (IQR, 17.1-19.7 weeks) for term births and 9.4 weeks (IQR, 6.9-10.7 weeks) for preterm births in the study cohort and 9.0 weeks (IQR, 8.1-9.9 weeks) for term births in the reference cohort (Table 1).[13]

Table 1. Baseline characteristics at mother and infant level for preterm/term mother-infant-pairs.

	Maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA		**Maternal Tdap-vaccination between $30^{0/7}$-$33^{0/7}$w GA**
	Preterm birth	**Term birth**	**Term birth (reference cohort)**
	n=73[a]	**n=66[a]**	**n=55[a]**
Maternal age at delivery (years); mean (sd)	31.4 (3.8)	31.7 (4.0)	32.6 (3.3)
Gestational age at maternal immunization (weeks); median [IQR]	22.9 [22.0-23.4]	22.0 [20.9-23.1]	31.1 [30.5-31.7]
Pregnancy duration (weeks); median [IQR]	32.1 [29.5-33.0]	40.6 [39.8-41.0]	40.3 [39.1-41.0]
Pregnancy duration; n (%)			
$25^{2/7}$-$27^{6/7}$ weeks gestational age	13 (17.8)	NA	NA
$28^{0/7}$-$31^{6/7}$ weeks gestational age	25 (34.2)	NA	NA
$32^{0/7}$-$34^{6/7}$ weeks gestational age	35 (47.9)	NA	NA
$37^{0/7}$-$39^{6/7}$ weeks gestational age	NA	21 (31.8)	23 (41.8)
$40^{0/7}$-$42^{0/7}$ weeks gestational age	NA	45 (68.2)	32 (58.2)
Interval between maternal immunization and delivery (weeks); median [IQR]	9.4 [6.9-10.7]	18.3 [17.1-19.7]	9.0 [8.1-9.9]
Multiple pregnancy; n (%)[b]			
No	45 (78.1)	66 (100.0)	55 (100.0)
Yes; twins	13 (19.2)	0 (0.0)	0 (0.0)
Yes; triplets	2 (2.7)	0 (0.0)	0 (0.0)
Sex; n (%)			
Male	35 (45.5)	38 (57.6)	22 (40.0)
Female	42 (54.5)	28 (42.4)	33 (60.0)
Birthweight (grams); mean (sd)[c]	1631 (499)	3622 (430)	3446 (481)
Birthweight percentile corrected for gestational age; mean (sd)[c]	38.8 (31.5)	53.1 (27.8)	42.4 (28.0)
Age at blood sampling (days); mean (sd)[d]	55.2 (6.2)	61.0 (3.0)	61.4 (2.1)

a: 73 preterm infants born to 60 mothers (due to multiple pregnancies) donated a blood sample at two months of age, as did 66 term infants plus 55 term infants in the reference cohort. b: 7 dichorionic-diamniotic twins, 4 monochorionic-diamniotic twins, 2 monochorionic-monoamniotic twins, 2 trichorionic-triamniotic triplets. Numbers add up to 60 infants (including siblings makes 77) for the total number mother-infant-pairs, but only 73 of 77 infants donated a blood sample at two months of age. c: Birthweight and birthweight percentiles were presented for firstborn infant only in case of multiple pregnancy. d: [Two-month] blood samples were drawn as close as possible to [infant] immunization but may have been performed earlier than at two months of age because in the Netherlands, routine preterm primary vaccinations are administered between 6-9 weeks after birth.

At 2 months of age in term infants, the anti-PT GMC after maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation (14.7 IU/mL; 95% CI, 10.6-20.4 IU/mL) was significantly lower than the GMC in the reference cohort after Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation (27.3 IU/mL; 95% CI, 20.1-37.1 IU/mL) (Table 2 and Figure 2). The GMR was 0.54 (95% CI, 0.34-0.85), with the 2.5% bound of the 95% CI at 0.34 (97.5% bound at 0.85) refuting noninferiority requirements.

At 2 months of age after maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation, no significant differences in anti-PT GMCs were observed in preterm infants compared with term infants (11.2 IU/mL [95% CI, 8.1-15.3 IU/mL] vs 14.7 IU/mL [95% CI, 10.6-20.4 IU/mL]) (P = .23) (Table 2 and Figure 3).

In term infants at 2 months of age, besides anti-PT levels, the GMC of IgG against Prn was significantly lower after Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation compared with $30^{0/7}$ to $33^{0/7}$ weeks' gestation (59.8 IU/mL [95% CI, 38.4-93.0 IU/mL] vs 110.3 IU/mL [95% CI, 71.6-170.0 IU/mL]). No differences in GMCs were observed for FHA, DT, or TT for term infants in the study compared with the reference cohort (Table 2 and Figure 2). In preterm infants compared with term infants at age 2 months after maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation, GMCs were significantly lower for FHA (48.8 IU/mL [95% CI, 37.3-63.8 IU/mL] vs 83.1 IU/mL [95% CI, 63.6-109.1 IU/mL]) and TT (1.2 IU/mL [95% CI, 1.0-1.5 IU/mL] vs 1.5 IU/mL [95% CI, 1.2-1.9 IU/mL]), whereas no significant differences were observed for Prn and DT (Table 2 and Figure 3).

In umbilical cord serum samples from term offspring, significantly lower GMCs were observed when mothers received Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation compared with $30^{0/7}$ and $33^{0/7}$ weeks' gestation for PT (58.6 IU/mL [95% CI, 46.4-74.2 IU/mL] vs 125.1 IU/mL [95% CI, 94.0-166.3 IU/mL]) and Prn (295.5 IU/mL [95% CI, 216.7-402.8 IU/mL] vs 500.5 IU/mL [95% CI, 322.5-776.7 IU/mL]). No differences were observed for FHA, DT, and TT IgG levels (Table 2 and Figure 2). In umbilical cord serum samples, GMCs from preterm offspring compared with term offspring following maternal Tdap vaccination between $20^{0/7}$

and $24^{0/7}$ weeks' gestation were significantly lower for FHA (193.5 IU/mL [95% CI, 155.2-241.3 IU/mL] vs 295.2 IU/mL [95% CI, 249.1-349.9 IU/mL]) and Prn (143.7 IU/mL [95% CI, 97.3-212.4 IU/mL] vs 295.5 IU/mL [95% CI, 216.7-402.8 IU/mL]). No differences between term and preterm offspring were observed for PT, DT and TT (Table 2 and Figure 3).

Comparing antibody levels at delivery among mothers of term offspring in the study and reference group, the anti-PT GMC at delivery was significantly higher in the reference group (61.8 IU/mL [95% CI, 46.8-81.7 IU/mL] vs 32.9 IU/mL [95% CI, 26.0-41.6 IU/mL]). No differences for the other Tdap antigens were found (Table 2 and Figure 2). Comparing preterm and term mother-infant pairs following Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation, mothers had significantly higher GMCs after preterm than term delivery for all antigens (eg, PT 60.4 IU/mL [95% CI, 44.1-82.7 IU/mL] vs 32.9 IU/mL [95% CI, 26.0-41.6 IU/mL]) except Prn (Table 2 and Figure 3). Sensitivity analyses using a Tdap vaccination cutoff of February 27, 2020, the first day of COVID-19 social distancing measures in the Netherlands, were conducted and found no differences in antibody levels after birth among mothers or infants before vs during COVID-19-measures.

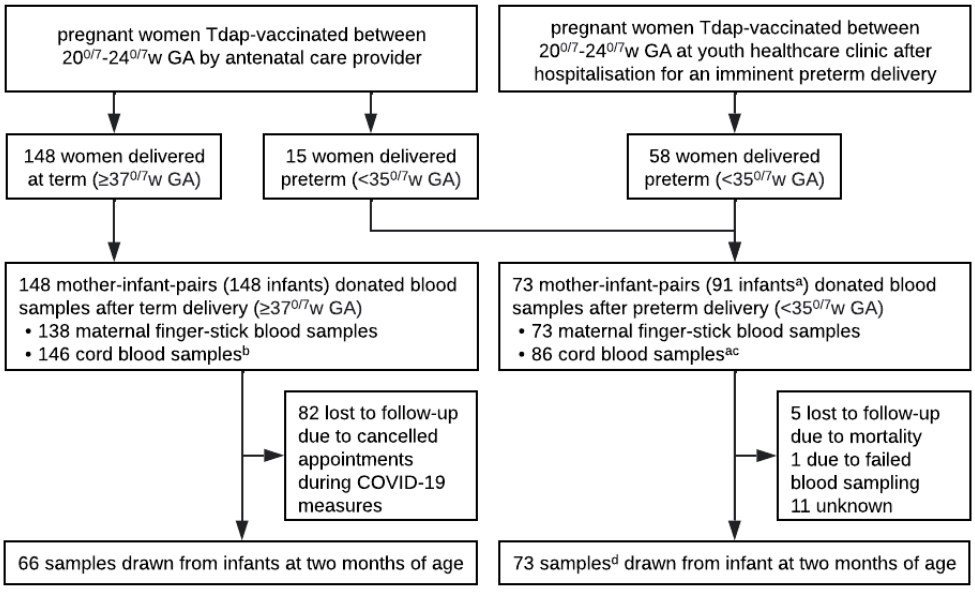


Figure 1. Flow chart of study procedures.

GA; gestational age. a: including 14 twins and 2 triplets, of whom one sample was not drawn due to perinatal death. b: 2 infants donated sample at two months but no cord blood sample. c: 4 infants donated sample at two months but no cord blood sample. d: 73 infants from 60 mothers donated a blood sample at two months of age.

Table 2. Geometric mean concentrations and ratios with 95% confidence intervals in preterm/term infants with mothers vaccinated $20^{0/7}$-$24^{0/7}$w GA and term infants with mothers vaccinated $30^{0/7}$-$33^{0/7}$w GA.

	Maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA (general cohort)		**Maternal Tdap-vaccination between $30^{0/7}$-$33^{0/7}$w GA (reference cohort)**				
	Delivery between $25^{2/7}$-$34^{6/7}$w GA (preterm)	**Delivery between $37^{0/7}$-$42^{0/7}$w GA (at term)**	**Delivery between $37^{0/7}$-$42^{0/7}$w GA (at term)**	**GMR at term (general cohort) vs at term (reference cohort)**	**p-value**	**GMR preterm vs at term**	**p-value**
Mother at delivery	**n=73**	**n=138**	**n=55**				
Anti-Pertussis toxin	60.4 (44.1-82.7)	32.9 (26.0-41.6)	61.8 (46.8-81.7)	0.53 (0.35-0.80)	<0.001	1.84 (1.24-2.72)	0.002
Anti-Filamentous hemagglutinin	220.5 (171.5-283.5)	161.1 (135.5-191.5)	163.4 (132.5-204.6)	0.99 (0.73-1.34)	0.920	1.37 (1.02-1.84)	0.040
Anti-Pertactin	203.1 (134.6-306.4)	176.5 (129.9-239.8)	286.0 (182.4-448.3)	0.62 (0.35-1.08)	0.075	1.15 (0.69-1.92)	0.585
Anti-Diphtheria toxoid	0.62 (0.50-0.77)	0.30 (0.24-0.37)	0.35 (0.26-0.47)	0.85 (0.58-1.24)	0.353	2.01 (1.50-2.91)	<0.001
Anti-Tetanus toxoid	5.58 (4.55-6.84)	3.32 (2.88-3.83)	3.53 (2.99-4.16)	0.94 (0.74-1.21)	0.588	1.68 (1.31-2.14)	<0.001

Table 2. Continued.

	Maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA (general cohort)		Maternal Tdap-vaccination between $30^{0/7}$-$33^{0/7}$w GA (reference cohort)				
	Delivery between $25^{2/7}$-$34^{6/7}$w GA (preterm)	Delivery between $37^{0/7}$-$42^{0/7}$w GA (at term)	Delivery between $37^{0/7}$-$42^{0/7}$w GA (at term)	GMR at term (general cohort) vs at term (reference cohort)	p-value	GMR preterm vs at term	p-value
Infant cord blood	**n=86**	**n=146**	**n=54**				
Anti-Pertussis toxin	52.8 (40.7-68.6)	58.6 (46.4-74.2)	125.1 (94.0-166.3)	0.47 (0.31-0.72)	<0.001	0.90 (0.63-1.30)	0.628
Anti-Filamentous hemagglutinin	193.5 (155.2-241.3)	295.2 (249.1-349.9)	330.9 (261.2-419.3)	0.89 (0.65-1.22)	0.430	0.66 (0.50-0.87)	0.006
Anti-Pertactin	143.7 (97.3-212.4)	295.5 (216.7-402.8)	500.5 (322.5-776.7)	0.59 (0.33-1.05)	0.049	0.49 (0.30-0.80)	0.022
Anti-Diphtheria toxoid	0.52 (0.42-0.65)	0.48 (0.39-0.59)	0.64 (0.48-0.86)	0.74 (0.50-1.09)	0.093	1.10 (0.80-1.52)	0.403
Anti-Tetanus toxoid	5.17 (4.20-6.36)	5.95 (5.15-6.88)	7.39 (6.19-8.82)	0.81 (0.62-1.04)	0.057	0.87 (0.68-1.11)	0.132

Table 2. Continued.

	Maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA (general cohort)		Maternal Tdap-vaccination between $30^{0/7}$-$33^{0/7}$w GA (reference cohort)				
	Delivery between $25^{2/7}$-$34^{6/7}$w GA (preterm)	Delivery between $37^{0/7}$-$42^{0/7}$w GA (at term)	Delivery between $37^{0/7}$-$42^{0/7}$w GA (at term)	GMR at term (general cohort) vs at term (reference cohort)	p-value	GMR preterm vs at term	p-value
Infant at 2m of age	**n=73**	**n=66**	**n=55**				
Anti-Pertussis toxin	11.2 (8.1-15.3)	14.7 (10.6-20.4)	27.3 (20.1-37.1)	0.54 (0.34-0.85)	0.005	0.76 (0.48-1.20)	0.231
Anti-Filamentous hemagglutinin	48.8 (37.31-63.8)	83.1 (63.6-109.1)	83.7 (67.4-103.9)	0.99 (0.70-1.42)	0.967	0.59 (0.40-0.86)	0.009
Anti-Pertactin	38.9 (24.7-61.5)	59.8 (38.4-93.0)	110.3 (71.6-170.0)	0.54 (0.29-1.01)	0.045	0.65 (0.35-1.23)	0.249
Anti-Diphtheria toxoid	0.11 (0.08-0.14)	0.12 (0.09-0.16)	0.13 (0.10-0.17)	0.89 (0.59-1.35)	0.570	0.93 (0.63-1.37)	0.727
Anti-Tetanus toxoid	1.19 (0.95-1.50)	1.53 (1.24-1.89)	1.67 (1.42-1.97)	0.92 (0.70-1.21)	0.516	0.78 (0.57-1.06)	0.029

GA; gestational age, GMR; geometric mean concentration ratio. Geometric mean concentrations are presented in international units per milliliter. Women vaccinated between $20^{0/7}$-$24^{0/7}$w GA who delivered term or preterm infants were included in the current study; women vaccinated between $30^{0/7}$-$33^{0/7}$w GA who delivered term infants were included in the reference cohort.

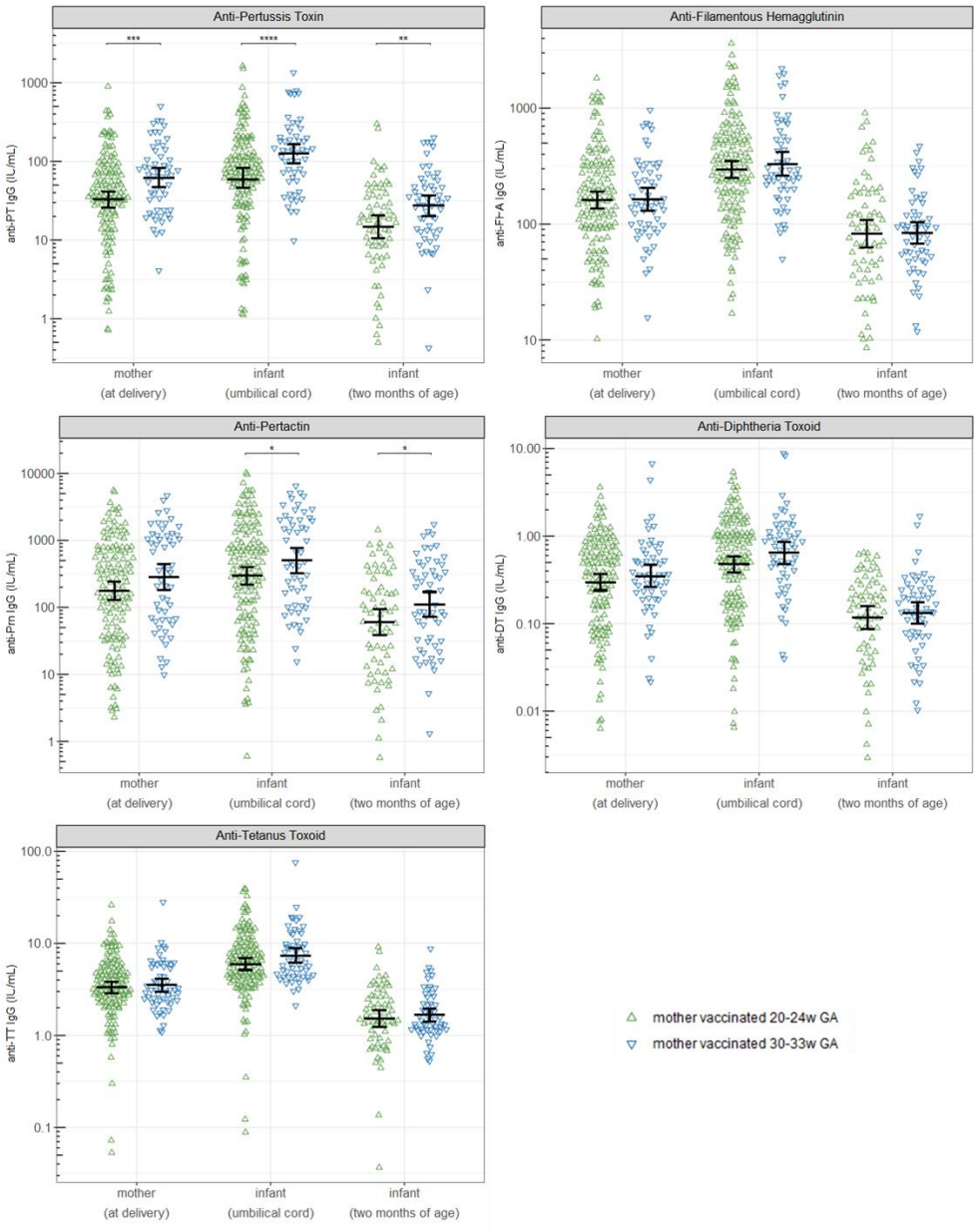


Figure 2. Individual IgG-antibody concentrations and GMCs after second- vs third-trimester Tdap-vaccination in term mother-infant-pairs at different timepoints.

DT; diphtheria toxoid, FHA; filamentous hemagglutinin, GA; gestational age, GMC; geometric mean concentration, IU/mL; international units per milliliter, Prn; pertactin, PT; pertussis toxin, TT; tetanus toxoid. Whiskers represent GMCs with corresponding 95% confidence intervals. Labels are presented only in case of a significant effect. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

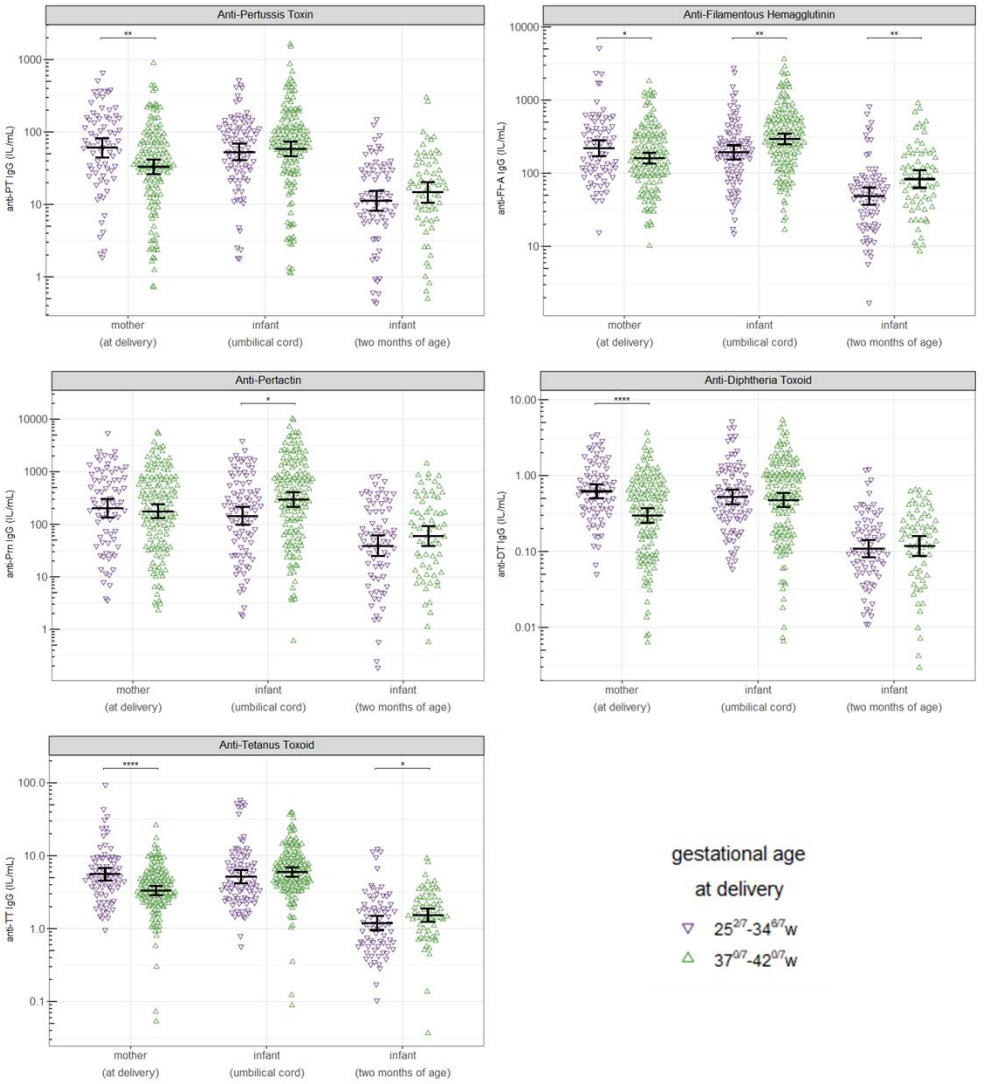


Figure 3. Individual IgG-antibody concentrations and GMCs after second-trimester Tdap-vaccination in term vs preterm mother-infant-pairs at different timepoints.

DT; diphtheria toxoid, FHA; filamentous hemagglutinin, GA; gestational age, GMC; geometric mean concentration, IU/mL; international units per milliliter, Prn; pertactin, PT; pertussis toxin, TT; tetanus toxoid. All women were vaccinated between $20^{0/7}$-$24^{0/7}$w GA. Whiskers represent GMCs with corresponding 95% confidence intervals. Labels are presented only in case of a significant effect. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Discussion

In this prospective cohort study, anti-PT IgG levels in term infants at 2 months of age following maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation were inferior to those in the group with Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation, with an approximate 2-fold reduction in GMCs of anti-PT IgG levels. As long as the mechanisms of protection following maternal Tdap vaccination are not fully understood and no correlate of protection is available, anti-PT IgG levels are often used in studies like ours as surrogate markers for protection.[17] Anti-PT levels in umbilical cord blood are correlated with protection against pertussis,[19] and lower anti-PT IgG levels may point to less protection against pertussis in newborns. We also observed a reduction in anti-Prn antibody levels after maternal Tdap vaccination between 20 and 24 weeks' gestation compared with the reference group.

The GA at which to administer maternal Tdap vaccination for the highest antibody transfer may vary per vaccine antigen. Many studies have suggested that Tdap vaccination between $27^{0/7}$ and $30^{0/7}$ weeks' gestation results in maximal pertussis-specific antibody levels and avidity in term offspring, though these studies provided no data on Tdap vaccination before 24 weeks' gestation.[4,7,20-25] In contrast, an observational Swiss study suggested that Tdap vaccination earlier in pregnancy led to higher maternal antibody transfer, potentially because of the longer transfer time before delivery.[10] The recent 'Optimising the Timing of Whooping Cough Immunisation in Mums (OpTIMUM) randomized clinical trial' observed the highest pertussis-specific IgG antibody levels in umbilical cord serum when mothers received the Tdap vaccine early in the third trimester (28-32 weeks' gestation) compared with earlier than 24 weeks' and 24 to 27 weeks' gestation.[6] Notably, the number of preterm offspring included in that study was too small to draw conclusions for this most vulnerable group (15 [4%]; 5 per study group).[6]

The reduction in anti–*B. pertussis* antibodies in offspring following maternal Tdap vaccination before 24 weeks' gestation may possibly be explained by the fact that peak levels of anti–*B. pertussis* antibodies following vaccination are achieved when maternofetal antibody transfer is still suboptimal. This appears not to be compensated by the increased time of around 9 weeks for transport until delivery.

Based on epidemiological studies, a minimum of 2 to 4 weeks between maternal Tdap vaccination and delivery seems required for protection of term offspring against clinical pertussis.[6] Up to 7 to 8 weeks was estimated to result in optimal antibody transfer.[5] Nevertheless, even in the case of a similar 9-week time interval between maternal Tdap vaccination and delivery in this study, GMCs in preterm offspring following maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$

weeks' gestation were at least 2-fold lower than those in term offspring from the reference group following maternal Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation. Also, while a longer interval in case of maternal Tdap vaccination between 20 and 24 weeks' gestation was associated with almost similar anti-PT antibody levels in term and preterm offspring after a time interval of 9 weeks and 18 weeks, respectively, a significant reduction in anti-PT levels but also anti-FHA and anti-Prn levels compared with Tdap vaccination between $30^{0/7}$ and $33^{0/7}$ weeks' gestation was observed. The OpTIMUM trial also showed significantly lower anti-PT antibodies after maternal Tdap vaccination at $24^{0/7}$ weeks' gestation or earlier.[6]

In a study from Belgium,[7] maternal Tdap vaccination at around 27 weeks' gestation resulted in improved maternal-derived, pertussis-specific antibody levels in preterm offspring, potentially due to receiving the vaccine at a time in pregnancy with a long enough interval before delivery together with a postvaccination antibody peak during the third trimester that has improved antibody transfer compared with the second trimester. This is relevant for most preterm offspring because currently, 84% of all preterm newborns in the Netherlands are delivered at or after 32 weeks' gestation.[26]

In the UK, timing of Tdap vaccination changed in 2016 from 28 weeks' to 16 weeks' gestation onward. A subsequent analysis of data on pertussis cases in the hospital showed that the effectiveness of maternal Tdap vaccination against pertussis-related hospitalization in infants had remained high.[27] It must be noted that the overall maternal Tdap vaccination coverage over the period of the study also increased, which might have contributed to robustly high maternal Tdap vaccine effectiveness rates. With an undefined correlate of protection, studies like ours cannot draw conclusions on clinical effectiveness of maternal Tdap vaccination at or before 24 weeks' gestation. Epidemiological studies on effectiveness with data stratified for GA at birth are required.

While protection against severe pertussis following maternal Tdap vaccination has been confirmed by many observational studies,[8,9] important knowledge gaps in the protective mechanisms remain. In addition to quantitative antibody levels, quality and functionality of anti–*B. pertussis* antibodies may contribute to protection against clinical pertussis, as may maternal immune cells, such as T cells, are transferred to the offspring during pregnancy and may vary with timing of maternal vaccination.[28-30] To our knowledge, the present study is the first to investigate transplacental antibody transfer following maternal Tdap vaccination before $24^{0/7}$ weeks' gestation in a large group of preterm- and early- to late-term infants up to the age of their first vaccinations and to compare antibody transfer with a well-defined cohort of 55 mother-infant pairs after Tdap vaccination

between $30^{0/7}$ and $33^{0/7}$ weeks' gestation.

Limitations

This study has limitations. Most importantly, the term offspring from the reference cohort were recruited within different periods. The present study was performed partially during nonpharmaceutical COVID-19 interventions, with reduced *B. pertussis* circulation compared with the 2014 to 2016 inclusion period of the reference cohort.[31] Lower endemic *B. pertussis* transmission might result in reduced preexisting antibody levels due to a lack of boosting in women of childbearing age[32] and may have impacted the antibody response to maternal Tdap vaccination. Sensitivity analyses with a Tdap vaccination cutoff at February 27, 2020, the first day of COVID-19 social distancing measures in the Netherlands, yielded no differences in antibody levels in mothers or infants after birth before and during COVID-19-measures in the present study. The vaccination history of mothers in the study and reference cohorts were similar. Starting in 1957 (ie, the start of the Dutch NIP), a whole-cell pertussis vaccine was used for infant vaccinations. In 1996, an acellular pertussis component was added to the DT-IPV booster dose administered at age 4 years. All participating mothers were born before 2005, the year when the infant acellular pertussis–boosted vaccine replaced infant whole-cell pertussis vaccines. In the near future, more pregnant women will receive the acellular pertussis primary or booster vaccine. This may impact anti-pertussis immune status and response to maternal Tdap vaccination.[33]

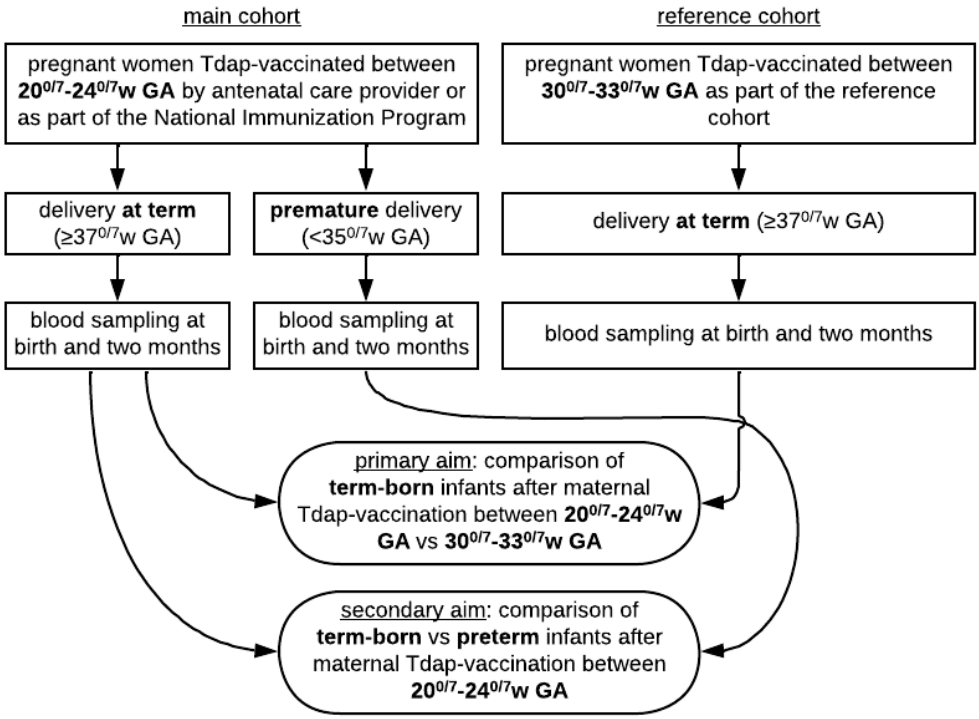
We did not study the antibody response to Tdap vaccination in mothers vaccinated earlier vs later during pregnancy. Potential differences may exist. We found that maternal antibodies at delivery following Tdap vaccination before 24 weeks' gestation were significantly higher with a shorter interval between Tdap vaccination and delivery, suggesting a rapid decline after peak levels following vaccination. Another limitation is the rate of loss to follow-up for samples. We included more term and preterm infants compared with other studies, but many appointments for blood sample obtainment at 2 months of age were cancelled due to COVID-19–related safety measures, resulting in large dropout rates among 2-month-old infants. However, samples from 66 term and 73 preterm infants yielded enough power to assess noninferiority. The dropout group at age 2 months was not selective and not expected to affect results. Finally, we performed a sensitivity analysis to compare mothers with imminent preterm labor recruited on presentation at the hospital with other mothers of preterm offspring vaccinated as part of the study (n = 46 vs 14). We found no statistically significant differences, but differences in clinical baseline factors that may correlate with preterm labor may

have occurred. However, we had no clinical data to compare these 2 groups in detail.

Conclusions

In this cohort study, maternal Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation compared with $30^{0/7}$ and $33^{0/7}$ weeks' gestation was associated with significantly lower anti-PT antibody levels in 2-month-old term and preterm infants despite a similar interval between maternal vaccination and delivery in preterm infants after Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' gestation and term infants after $30^{0/7}$ and $33^{0/7}$ weeks' gestation. Further epidemiological research should determine whether maternal Tdap vaccination before 24 weeks' gestation provides sufficient protection against clinical pertussis both in term and preterm infants as long as no correlate of protection is available.

Supplementary materials



Supplemental eFigure 1. Comparisons for the primary and secondary aim of this study.

References

1. WHO pertussis. 2022. https://www.who.int/health-topics/pertussis.
2. Althouse BM, Scarpino SV. Asymptomatic transmission and the resurgence of Bordetella pertussis. *BMC Med* 2015; **13**: 146.
3. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; **36**(5): 248-55.
4. Healy CM, Rench MA, Swaim LS, et al. Association Between Third-Trimester Tdap Immunization and Neonatal Pertussis Antibody Concentration. *JAMA* 2018; **320**(14): 1464-70.
5. Gomme J, Wanlapakorn N, Ha HTT, Leuridan E, Herzog SA, Maertens K. The Impact of Timing of Pertussis Vaccination During Pregnancy on Infant Antibody Levels at Birth: A Multi-Country Analysis. *Front Immunol* 2022; **13**: 913922.
6. Calvert A, Amirthalingam G, Andrews N, et al. Optimising the timing of whooping cough immunisation in mums (OpTIMUM) through investigating pertussis vaccination in pregnancy: an open-label, equivalence, randomised controlled trial. *Lancet Microbe* 2023.
7. Maertens K, Orije MRP, Herzog SA, et al. Pertussis immunization during pregnancy: assessment of the role of maternal antibodies on immune responses in term and preterm born infants. *Clin Infect Dis* 2021.
8. Kandeil W, van den Ende C, Bunge EM, Jenkins VA, Ceregido MA, Guignard A. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. *Expert Rev Vaccines* 2020; **19**(7): 621-38.
9. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. *Pediatrics* 2017; **139**(5).
10. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *Clin Infect Dis* 2016; **62**(7): 829-36.
11. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization. *Clin Infect Dis* 2017; **64**(8): 1129-32.
12. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. *Arch Dis Child* 2017.
13. Barug D, Pronk I, van Houten MA, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. *Lancet Infect Dis* 2019; **19**(4): 392-401.
14. Immink MM, Bekker MN, de Melker HE, Rots NY, Sanders EAM, van der Maas NAT. Study protocol of the PIMPI-project, a cohort study on acceptance, tolerability and immunogenicity of second trimester maternal pertussis immunization in relation to term and preterm infants. *BMC Infect Dis* 2021; **21**(1): 897.
15. Boostrix ®, Official Product Information. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Boostrix/pdf/BOOSTRIX.PDF.
16. van Gageldonk PG, van Schaijk FG, van der Klis FR, Berbers GA. Development and validation of a multiplex immunoassay for the simultaneous determination of serum antibodies to Bordetella pertussis, diphtheria and tetanus. *J Immunol Methods* 2008; **335**(1-2): 79-89.
17. Callender M, Harvill ET. Maternal vaccination: shaping the neonatal response to pertussis. *Front Immunol* 2023; **14**: 1210580.
18. Halekoh U, Højsgaard S, Yan J. The R Package geepack for Generalized Estimating Equations. *Journal of Statistical Software* 2006; **15**(2): 11.
19. Cherry JD. Immunity to pertussis. *Clin Infect Dis* 2007; **44**(10): 1278-9.
20. Abu-Raya B, Forsyth K, Halperin SA, et al. Vaccination in Pregnancy against Pertussis: A Consensus Statement on Behalf of the Global Pertussis Initiative. *Vaccines (Basel)* 2022; **10**(12).
21. Abu-Raya B, Giles ML, Kollmann TR, Sadarangani M. The Effect of Timing of Tetanus-Diphtheria-Acellular Pertussis Vaccine Administration in Pregnancy on the Avidity of Pertussis Antibodies. *Front Immunol* 2019; **10**: 2423.
22. Naidu MA, Muljadi R, Davies-Tuck ML, Wallace EM, Giles ML. The optimal gestation for pertussis vaccination during pregnancy: a prospective cohort study. *Am J Obstet Gynecol* 2016; **215**(2): 237 e1-6.

23. Abu Raya B, Srugo I, Kessel A, et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels - a prospective study. *Vaccine* 2014; **32**(44): 5787-93.
24. Abu Raya B, Bamberger E, Almog M, Peri R, Srugo I, Kessel A. Immunization of pregnant women against pertussis: the effect of timing on antibody avidity. *Vaccine* 2015; **33**(16): 1948-52.
25. Abu Raya B, Srugo I, Bamberger E, Kessel A. The avidity of pertussis antibodies following gestational acellular pertussis immunization: Reply to Maertens. *Vaccine* 2015; **33**(42): 5490-1.
26. Peristat. 2021. https://www.peristat.nl/.
27. Tessier E, Campbell H, Ribeiro S, et al. Impact of extending the timing of maternal pertussis vaccination on hospitalized infant pertussis in England, 2014 - 2018. *Clin Infect Dis* 2020.
28. Cherry JD, Gornbein J, Heininger U, Stehr K. A search for serologic correlates of immunity to Bordetella pertussis cough illnesses. *Vaccine* 1998; **16**(20): 1901-6.
29. Hellwig SM, Rodriguez ME, Berbers GA, van de Winkel JG, Mooi FR. Crucial role of antibodies to pertactin in Bordetella pertussis immunity. *J Infect Dis* 2003; **188**(5): 738-42.
30. Marcellini V, Piano Mortari E, Fedele G, et al. Protection against Pertussis in Humans Correlates to Elevated Serum Antibodies and Memory B Cells. *Front Immunol* 2017; **8**: 1158.
31. Middeldorp M, van Lier A, van der Maas N, et al. Short term impact of the COVID-19 pandemic on incidence of vaccine preventable diseases and participation in routine infant vaccinations in the Netherlands in the period March-September 2020. *Vaccine* 2021; **39**(7): 1039-43.
32. Reicherz F, Golding L, Lavoie PM, Abu-Raya B. Decay of anti-Bordetella pertussis antibodies in women of childbearing age following COVID-19 non-pharmaceutical measures. *Vaccine* 2022; **40**(27): 3746-51.
33. Havers FP, Skoff TH, Rench MA, et al. Maternal Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccination During Pregnancy: Impact on Infant Anti-Pertussis Antibody Concentrations by Maternal Pertussis Priming Series. *Clin Infect Dis* 2023; **76**(3): e1087-e93.

CHAPTER 4

Decay rates of maternal tetanus, diphtheria and pertussis antibody levels in early- and moderate-to-late preterm and term infants at birth and at 2 months

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Abstract

Post-hoc analysis of maternally-derived antibodies at birth and age 2 months following second trimester maternal Tdap-vaccination between 20-24 weeks gestational age (GA), showed a faster decay-rate of Tdap-related IgG in early-preterms born before 32w GA compared to moderate-to-late-preterms and full-terms. This is different from previous studies and merits further research.

Brief report

Before the first immunizations against pertussis at age 2-3 months (mo), infants, and particularly preterms, remain vulnerable for developing severe pertussis.[1] Enhanced maternally derived anti-pertussis antibody levels in infants following maternal tetanus-diphtheria-and-acellular-pertussis (Tdap) vaccination, was shown to be 90% effective in protection of newborns against pertussis during this period.[2] The height of maternally-derived anti-pertussis antibodies at birth and at 2mo-of-age after maternal Tdap-vaccination is determined by many factors, e.g. gestational age (GA), the time interval between maternal vaccination and birth, placental function and postnatal antibody decay.[3,4] Therefore, anti-pertussis antibodies at 2mo may differ between full-terms and preterms.[5] However, knowledge about the persistence of pertussis-specific vaccine-induced maternal antibodies, in particular in the case of early second trimester Tdap-vaccination and early-preterms born before 32w GA, is limited.

We recently reported on a prospective study on transplacental IgG transfer following maternal Tdap-vaccination between 20-24w GA, i.e. early during the advised immunization period, in full-terms and preterms.[6] We compared anti-B.pertussis-IgG levels at birth and 2mo. In this post-hoc analysis, we compared antibody levels in cord blood and at 2mo between early- and moderate-to-late-preterms versus full-terms, and estimated Tdap-specific antibody decay-rates between birth and 2mo-of-age in these groups.

For the analysis, three groups were defined: mother-infant pairs of early-preterms (birth $25^{0/7}$-$31^{6/7}$w GA), moderate-to-late-preterms ($32^{0/7}$-$34^{6/7}$w GA) and full-terms ($37^{0/7}$-$42^{0/7}$w GA). We did not include 35-36w GA preterms because their antibody transfer resembles transfer in full-terms due to active transplacental transport.[7] Blood was collected from mothers within 24h after delivery, from the umbilical cord and from infants at age 6-9w if premature and 2mo±5d in full-terms and in all cases before the first pertussis immunization. The study was approved by the Central Committee on Research Involving Human Subjects (NL66966.000.18). Informed consent was obtained from parents or legal guardians.[8,9]

IgG-antibody concentrations against pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (Prn), and toxoids of diphtheria (DT) and tetanus (TT) were determined as described[10] and were log-transformed. Geometric mean concentrations (GMCs) with corresponding 95%CI were calculated. GMC-differences between the groups and at different time-points were compared by utilizing a marginal generalized estimating equation model, taking into account the between-variation.

The decay-rate (i.e. time in which antibody concentrations decrease 2-fold) of

maternal antibodies in infants until 2mo-of-age was estimated with a linear mixed effects model of log^2-transposed antibody concentrations with random slope, adjusted for timeliness of blood sampling. The antibody decay-rate was expressed as the inverse of the regression slope in days. An infant was included in the analysis if measurements of Tdap-specific antibody concentrations for cord blood and 2mo were available, were above the lower-limit-of-quantification and indicated a decay. Baseline characteristics are reported as means and standard deviations or as absolute numbers and percentages. Comparison of baseline characteristics was done using either a t-test, Mann-Whitney U, or Fisher's exact test.

Complete data were available from 37 early- and 36 moderate-to-late-preterms and 66 full-terms (Supplementary table 1). Mean GA at Tdap-vaccination was 22.6w, 22.7w and 22.0w for mothers of early- and moderate-to-late-preterms and full-terms, respectively. This corresponded with mean time intervals between maternal Tdap-vaccination and delivery of 6.3w, 10.5w and 18.3w.

At age 2mo, anti-PT GMCs were 8.63IU/ml (95%CI 5.52-13.48; early-preterms), 14.58 (9.25-22.99; moderate-to-late-preterms) and 14.70 (10.58-20.41; full-terms) (Figure1). Though lower in early-preterms, differences between the small groups were non-significant. Anti-FHA and -Prn GMCs in early-preterms were significantly lower compared to moderate-to-late-preterms and full-terms (Supplementary table2; Figure1). Anti-TT GMC in early-preterms was significantly lower compared with full-terms, but not with moderate-to-late-preterms. For the anti-DT GMC, no significant differences were found between the groups.

In cord blood, no differences were observed for anti-PT GMCs: 56.24IU/ml (39.98-79.12), 49.30 (32.50-74.78) and 58.65 (46.38-74.16) for the groups. For anti-FHA and anti-Prn, GMC in early-preterms was significantly lower than in full-terms, but not compared with moderate-to-late-preterms (Supplementary table 2; Figure 1). For anti-DT GMC and anti-TT GMC, no significant differences were found.

In mothers of early-preterms, anti-PT GMC at delivery was 75.24IU/ml (48.90-115.79) compared with 47.64 (29.85-76.03; mothers of moderate-to-late-preterms) and 32.88 (26.01-41.57; mothers of full-terms) and associated with the time interval between Tdap-vaccination and delivery (data not shown). Maternal anti-FHA- and anti-Prn GMCs did not differ between the groups (Supplementary table 2; Figure 1). Anti-DT and -TT GMCs were significantly higher in mothers of early-preterms compared with mothers of moderate-to-late-preterms and full-terms.

Decay-rates of maternal antibodies were significantly faster in early-preterms compared with moderate-to-late-preterms or full-terms for all antigens, e.g. for PT, this was 21.7d vs 32.9d and 32.2d, respectively. No differences were found between moderate-to-late-preterms and full-terms (Table 1).

Table 1. Antibody decay estimates with corresponding 95% confidence intervals in number of days at which half of all measured antibody concentrations remained in early- and late-preterms and full-term infants.

IgG antibody	Delivery between $25^{0/7}$-$31^{6/7}$w GA	Delivery between $32^{0/7}$-$34^{6/7}$w GA	Delivery between $37^{0/7}$-$42^{0/7}$w GA
Anti-Pertussis toxin	21.7 (19.2-24.4)	32.6 (29.1-34.6)	32.1 (30.6-33.7)
Anti-Filamentous hemagglutinin	22.0 (20.0-24.5)	33.0 (30.2-36.5)	33.5 (32.1-35.0)
Anti-Pertactin	21.8 (19.6-24.5)	31.8 (28.4-33.6)	31.9 (30.4-33.6)
Anti-Diphtheria toxoid	20.8 (19.1-22.9)	28.7 (26.8-31.4)	29.4 (28.3-30.7)
Anti-Tetanus toxoid	22.0 (19.9-24.5)	29.3 (27.1-31.9)	30.8 (29.5-32.2)

GA, gestational age.

We recently described that maternal Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA resulted in almost similar antibody levels against PT, DT and TT at birth and 2mo-of-age between preterms (i.e. all infants born $25^{0/7}$-$34^{6/7}$w GA), compared with full-terms, although Tdap-vaccination before 24w GA resulted in at least two-fold lower anti-PT antibody levels compared with maternal Tdap-vaccination between $30^{0/7}$-$33^{0/7}$w GA.[6] Results of these post-hoc analyses of the study data suggest that Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA leads to lower Tdap-related antibody concentrations at 2mo-of-age in early-preterms but that levels in moderate-to-late-preterms born after 32w GA are very similar to full-terms. This would indicate that lower levels in early-preterms at age 2mo is not only explained by the sometimes lower maternally derived IgG levels at birth, but also by faster decay-rates of maternal antibodies in the first months of life.

When we compare our data with an individual participant data meta-analysis (n=1426, mainly full-terms), point-estimates of half-lives of Tdap-related antibodies ranged between 28.7d for anti-TT to 35.1d for anti-Prn, similar to the decay-rates we observed for moderate-to-late-preterms and full-terms, but different from the much faster decay rates of 21d we observed in early-preterms. The faster decay rate in early-preterms is in contrast with findings in preterms by Maertens et al., who reported longer half-lives of maternal Tdap-related IgG levels after birth in preterms vs full-terms.[11] Data of the Maertens study combined with another study on maternal Tdap-vaccination in term mother-infant-pairs performed in Thailand were included in a detailed study by Embacher et al. on determinants of half-lives of maternally-derived antibodies after Tdap-vaccination.

The authors found that being born at term, having a higher maternal antibody concentration at birth, an increased change in infant weight in the first two months of life and no breastfeeding shortened IgG half-life, whereas female sex and a longer interval between maternal vaccination and delivery were associated with an increased half-life. Taking all covariates from both studies together (if applicable), authors found longer half-lives in preterms vs full-terms, which differs from the shorter half-life in early-preterms in our post-hoc analysis. While the method to estimate decay rates in our study is rather similar to the studies from Embacher, Maertens and a study by Oguti et al.,[4,5,11] there are however important differences between our post-hoc study and the two studies Embacher used for analyses. First, in our study women were vaccinated much earlier during pregnancy (mean GA 22.6w, 22.7w and 22.0w for the three groups) compared with 29.3w (full-terms) and 28.8w (preterms) in Maertens et al. and 30.7w (full-terms) in the Thai study by Wanlapakorn et al. without preterms [11,12] Second, our early-preterms had a much lower GA with a mean GA at birth of 28.9w while this was 33.2w for moderate-to-late-preterms and 34.0w for all preterms described by Maertens et al.

Besides the lower gestational age of early-preterms and the earlier Tdap-vaccination around 22w, other factors like relative weight gain, more frequent blood-withdrawal and breastfeeding practices in early-preterms between birth and 2mo-of-age may have contributed to the contrasting results between our post-hoc analysis and the studies of Embacher and Maertens.[5,11] Furthermore, antibody concentrations at delivery were relatively high in mothers of early-preterms after maternal Tdap-vaccination before 24w GA, e.g. anti-PT GMC in mothers of early-preterms was 75.24 compared with 47.64 (mothers of moderate-to-late-preterms) and 32.88 (mothers of full-terms). Besides quantitative, also qualitative characteristics of maternally derived IgG antibodies may affect protection against pertussis and may be different following timing of maternal Tdap-vaccination and delivery.[13]

This study represents post-hoc analyses of a larger study investigating disease-specific transplacental antibody transfer following $20^{0/7}$-$24^{0/7}$w Tdap-vaccination in full-terms and all preterms born between 25w and 35w GA.[6] Our findings on early- and moderate-to-late-preterms therefore come with limited power and should be interpreted with caution.

In the Netherlands, infant DTaP-IPV-Hib-HepB-vaccinations are administered at 3, 5 and 12mo-of-age, provided that the mother was Tdap-vaccinated during pregnancy at least 14d before delivery and the infant is full-term. Preterms born before 37w GA obtain an additional dose between 6-9w-of-age. Further studies are needed to confirm similar antibody levels and IgG half-lives compared with full-

terms in case the child is born after 32w GA, and with a sufficient interval between maternal vaccination and delivery. This may impact vaccination strategies in case of moderate-to-late-preterm birth.

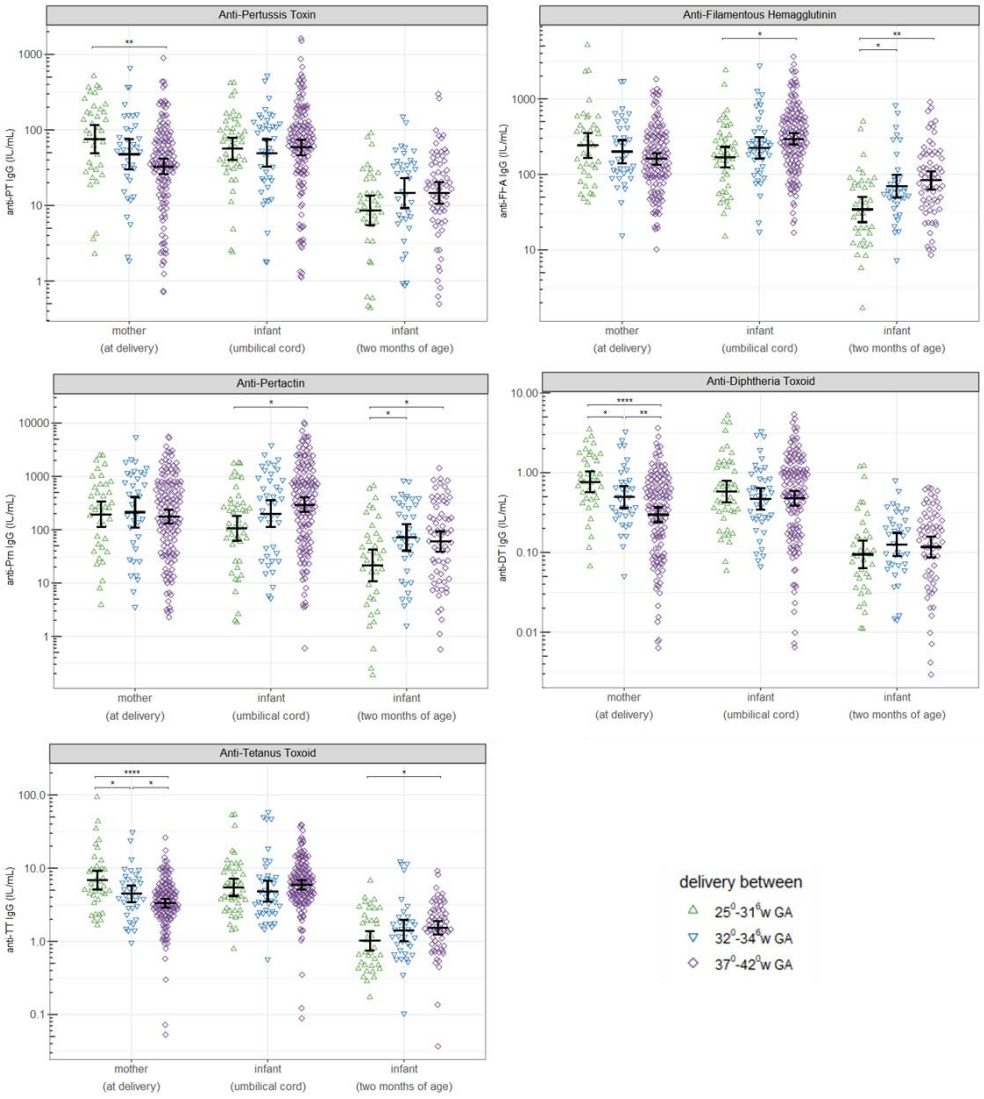

Figure 1. Individual IgG antibody concentrations and GMCs with 95%CI after $20^{0/7}$-$24^{0/7}$w GA Tdap-vaccination in preterm and term mother-infant-pairs at different timepoints. DT; diphtheria toxoid, FHA; filamentous hemagglutinin, GA; gestational age, GMC; geometric mean concentration, IU/mL; international units per milliliter, Prn; pertactin, PT; pertussis toxin, TT; tetanus toxoid. Whiskers represent GMCs with corresponding 95% confidence intervals. Difference labels are only presented in case of a significant effect. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

In conclusion, in early-preterms, Tdap-vaccination between $20^{0/7}$-$24^{0/7}$w GA may lead to threefold lower IgG antibody levels against several Tdap-included antigens at 2mo-of-age, due to lower levels at birth but also faster IgG decay-rates when born <$32^{0/7}$w GA, while moderate-to-late-preterms had similar antibody levels at birth and similar IgG decay-rates as full-terms.

Supplementary materials

Supplementary table 1. Baseline characteristics at maternal and neonatal level for early- and late-preterm and term mother-infant-pairs.

	Early-preterm birth ($25^{0/7}$-$31^{6/7}$w GA)	Late-preterm birth ($32^{0/7}$-$34^{6/7}$w GA)	Term birth ($37^{0/7}$-$42^{0/7}$w GA)
Mothers	**n=38[a]**	**n=35[a]**	**n=66[a]**
Maternal age at delivery (years); mean (sd)	30.9 (3.0)	31.9 (4.5)	31.7 (4.0)
Gestational age at maternal immunization (weeks); mean (sd)	22.6 (1.1)	22.7 (1.0)	22.0 (1.2)
Pregnancy duration (weeks); mean (sd)	28.9 (1.9)	33.2 (0.9)	40.6 (1.1)
Interval between maternal immunization and delivery (weeks); mean (sd)	6.3 (2.5)	10.5 (1.1)	18.3 (1.6)
Multiple pregnancy; n (%)[b]			
No	31 (81.6)	26 (74.3)	66 (100.0)
Yes; twins	5 (13.2)	9 (25.7)	0 (0.0)
Yes; triplets	2 (5.3)	0 (0.0)	0 (0.0)
Infants (at birth)	**n=47[a]**	**n=44[a]**	**n=64[a]**
Sex; n (%)			
Male	23 (48.9)	23 (52.3)	38 (57.6)
Female	24 (51.1)	21 (47.7)	28 (42.4)
Birthweight (grams); mean (sd)[c]	1243 (371)	1922 (374)	3622 (430)
Birthweight percentile corrected for gestational age; mean (sd)[d]	42.4 (33.6)	31.9 (30.0)	53.1 (27.8)
Age at blood sampling (days); mean (sd)	54.6 (6.9)	55.7 (5.4)	61.0 (3.0)

a: 73 preterm infants born to 60 mothers (due to multiple pregnancies) donated a blood sample at two months of age. 66 term infants donated a blood sample at two months of age. b: 7 dichorionic-diamniotic twins, 4 monochorionic-diamniotic twins, 2 monochorionic-monoamniotic twins, 2 trichorionic-triamniotic triplets. c: Birthweight and birthweight percentile was presented for firstborn infant only in case of multiple pregnancy. d: Blood samples were drawn shortest as possible before immunization but may be performed earlier than at two months of age because in the Netherlands, routine preterm primary vaccinations are administered between 6-9 weeks after birth. *$p<0.05$

Supplementary table 2. Geometric mean concentrations with 95% confidence intervals in early and moderate-to-late preterms and term-born infants of mothers who were vaccinated with Tdap between $20^{0/7}$-$24^{0/7}$GA.

	Delivery between $25^{2/7}$-$31^{6/7}$w GA	**Delivery between $32^{0/7}$-$34^{6/7}$w GA**	**Delivery between $37^{0/7}$-$42^{0/7}$w GA**
Mother at delivery	**n=38**	**n=35**	**n=138**
Anti-Pertussis toxin	75.24 (48.90-115.79)	47.64 (29.85-76.03)	32.88 (26.01-41.57)
Anti-Filamentous hemagglutinin	241.03 (165.97-350.03)	200.19 (141.14-283.93)	161.10 (135.52-191.52)
Anti-Pertactin	194.15 (112.92-333.84)	213.21 (110.94-409.74)	176.52 (129.93-239.81)
Anti-Diphtheria toxoid	0.77 (0.57-1.03)	0.49 (0.36-0.68)	0.30 (0.24-0.37)
Anti-Tetanus toxoid	6.84 (5.07-9.22)	4.47 (3.42-5.85)	3.32 (2.88-3.83)
Infant cord blood	**n=45**	**n=41**	**n=146**
Anti-Pertussis toxin	56.24 (39.98-79.12)	49.30 (32.50-74.78)	58.65 (46.38-74.16)
Anti-Filamentous hemagglutinin	169.30 (124.01-231.14)	224.10 (162.81-308.45)	295.19 (249.05-349.87)
Anti-Pertactin	106.36 (62.35-181.43)	200.15 (112.26-356.85)	295.45 (216.70-402.82)
Anti-Diphtheria toxoid	0.58 (0.42-0.80)	0.47 (0.35-0.64)	0.48 (0.39-0.59)
Anti-Tetanus toxoid	5.48 (4.18-7.19)	4.84 (3.49-6.72)	5.95 (5.15-6.88)
Infant at 2m of age	**n=37**	**n=36**	**n=66**
Anti-Pertussis toxin	8.63 (5.52-13.48)	14.58 (9.25-22.99)	14.70 (10.58-20.44)
Anti-Filamentous hemagglutinin	34.36 (23.28-50.69)	69.97 (49.40-99.11)	83.07 (63.25-109.11)
Anti-Pertactin	21.56 (10.88-42.73)	71.49 (40.49-126.24)	59.76 (38.42-92.97)
Anti-Diphtheria toxoid	0.09 (0.06-0.14)	0.13 (0.09-0.18)	0.12 (0.087-0.16)
Anti-Tetanus toxoid	1.02 (0.75-1.39)	1.40 (1.00-1.96)	1.53 (1.24-1.89)

GA; gestational age, GMC; Generalized mean concentration. Concentrations were presented in

international units per milliliter. Women vaccinated between $20^{0/7}$-$24^{0/7}$w GA were included in the current study, as opposed to women vaccinated between $30^{0/7}$-$33^{0/7}$w GA, who were included in the historical comparator study.

References

1. Kandeil W, van den Ende C, Bunge EM, Jenkins VA, Ceregido MA, Guignard A. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. *Expert review of vaccines* 2020: 1-18.
2. Vygen-Bonnet S, Hellenbrand W, Garbe E, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. *BMC Infect Dis* 2020; **20**(1): 136.
3. Voysey M, Kelly DF, Fanshawe TR, et al. The Influence of Maternally Derived Antibody and Infant Age at Vaccination on Infant Vaccine Responses : An Individual Participant Meta-analysis. *JAMA pediatrics* 2017.
4. Oguti B, Ali A, Andrews N, et al. The half-life of maternal transplacental antibodies against diphtheria, tetanus, and pertussis in infants: an individual participant data meta-analysis. *Vaccine* 2022; **40**(3): 450-8.
5. Embacher S, Maertens K, Herzog SA. Half-life Estimation of Pertussis-Specific Maternal Antibodies in (Pre)Term Infants After In-Pregnancy Tetanus, Diphtheria, Acellular Pertussis Vaccination. *J Infect Dis* 2023; **228**(11): 1640-8.
6. Immink MM, Bekker MN, de Melker HE, et al. Maternal Pertussis Immunization and Immunoglobulin G Levels in Early- to Late-Term and Preterm Infants. *JAMA Netw Open* 2024; **7**(7): e2424608.
7. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; **36**(5): 248-55.
8. Immink MM, Bekker MN, de Melker HE, Rots NY, Sanders EAM, van der Maas NAT. Study protocol of the PIMPI-project, a cohort study on acceptance, tolerability and immunogenicity of second trimester maternal pertussis immunization in relation to term and preterm infants. *BMC Infect Dis* 2021; **21**(1): 897.
9. Immink MM, Bekker MN, de Melker HE, et al. Maternal pertussis immunization before 24w of gestation and IgG-levels in term and preterm infants. *under review at JAMA* 2024.
10. van Gageldonk PG, van Schaijk FG, van der Klis FR, Berbers GA. Development and validation of a multiplex immunoassay for the simultaneous determination of serum antibodies to Bordetella pertussis, diphtheria and tetanus. *J Immunol Methods* 2008; **335**(1-2): 79-89.
11. Maertens K, Orije MRP, Herzog SA, et al. Pertussis immunization during pregnancy: assessment of the role of maternal antibodies on immune responses in term and preterm born infants. *Clin Infect Dis* 2021.
12. Wanlapakorn N, Maertens K, Chaithongwongwatthana S, et al. Assessing the reactogenicity of Tdap vaccine administered during pregnancy and antibodies to Bordetella pertussis antigens in maternal and cord sera of Thai women. *Vaccine* 2018; **36**(11): 1453-9.
13. Abu Raya B, Bamberger E, Almog M, Peri R, Srugo I, Kessel A. Immunization of pregnant women against pertussis: the effect of timing on antibody avidity. *Vaccine* 2015; **33**(16): 1948-52.

CHAPTER 5

Maternal and neonatal antibody levels upon pertussis vaccination in pregnant women on immune-modulating therapy for rheumatic disease

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Abstract

Objectives

While protection against pertussis following maternal tetanus-diphtheria-and-acellular-pertussis (Tdap) vaccination was demonstrated in healthy term-born infants, no evidence is available on Tdap vaccination in combination with immune-modulating therapy during pregnancy. In this pilot-study, we explored whether treatment with Tumor Necrosis Factor alpha inhibitors (TNFis) in pregnant patients with rheumatic disease interferes with Tdap vaccine responses and affects maternal anti-pertussis IgG antibody levels in newborns.

Methods

Patients were included by a rheumatologist during pregnancy in case they received maternal Tdap vaccination in the late-second or early-third trimester of pregnancy. Blood samples were obtained from mothers during the first pregnancy trimester, three months after delivery and from the umbilical cord. IgG antibody levels against Tdap-included antigens were measured using a bead-based multiplex immunoassay. Findings on patients exposed to TNFis were compared with those from TNFi-unexposed patients and with data from a historical comparator study among healthy Tdap vaccinated mother-infant-pairs (n=53).

Results

66 patients (46 exposed and 20 unexposed to TNFIs) were enrolled. No major differences in IgG antibody levels were observed between TNFi-exposed and unexposed mothers before maternal Tdap vaccination and three months after delivery. In cord sera however, antibody levels against pertussis toxin were significantly lower after TNFi-treatment (35.94IU/mL, 95%CI 20.68-62.45) compared with no TNFi-treatment of mothers with rheumatic disease (94.61IU/mL, 95%CI 48.89-183.07) and lower compared with a cohort of healthy mothers (125.12IU/mL, 95%CI 90.75-172.50). We observed similar differences for filamentous hemagglutinin, pertactin, tetanus toxoid, and diphtheria toxoid.

Conclusion

These preliminary data indicate no major differences in IgG antibody levels upon maternal Tdap vaccination in pregnant women with or without immune-modulating treatment, although our findings suggest that TNFis during pregnancy induce lower maternal anti-pertussis-specific protective antibody levels in newborns.

Introduction

Pertussis, also known as whooping cough, is an extremely contagious bacterial respiratory disease. The gram-negative bacterium *Bordetella pertussis* infiltrates respiratory epithelial cells and produces several kinds of toxins that interfere with secretion and bacterial clearance, causing the clinical symptoms of pertussis. The disease is especially dangerous in early infancy before start of the primary pertussis vaccination series, leaving newborns in the first months of life at increased risk for severe and potentially life-threatening complications. Endemic cycles of pertussis occur regularly and outbreaks have enhanced *B. pertussis* circulation over time and thereby pertussis infection in not fully vaccinated infants in the most recent years.[1-3] Asymptomatic adolescents and adults in the same household seem to be the main source of transmission to newborns.[4]

Maternal vaccination enhances protection against vaccine-preventable infectious diseases in infants during the very first months of life, as a result of transplacental transfer of protective IgG antibodies.[5-8] This process is mediated by the neonatal Fc receptor (FcRn) which is expressed on syncytiotrophoblast cells, and antibody transfer initiates between 12-17 weeks (w) of pregnancy with rates that increase throughout gestation.[5] Maternal vaccination against tetanus, diphtheria, and acellular pertussis (Tdap) during the third trimester of pregnancy was shown to offer an approximate 90% effectiveness in protection against severe clinical pertussis until infants reach the age of 2 to 3 months, before they receive primary vaccinations.[1,6,9] Nowadays, maternal Tdap vaccination is recommended by a growing number of countries, including the Netherlands.[10]

Current data on immunogenicity after maternal Tdap vaccination concern studies in healthy pregnant women, generally vaccinated during the third trimester.[7,11] No evidence about the effects of maternal Tdap vaccination is available regarding women on immune-modulating therapy for rheumatic diseases. Biological disease-modifying antirheumatic drugs (bDMARDs), e.g. treatment with Tumor Necrosis Factor inhibitors (TNFis), are widely used as treatment for rheumatic diseases, both during and outside pregnancy.[8] Recent studies have shown that the immune response upon the coronavirus vaccine is reduced in patients treated with immune-modulatory agents (including TNFi) for rheumatic disease.[12-16] However, the available evidence on potential hampering effects of TNFi-therapy on antibody responses to Tdap vaccination in men and non-pregnant women is contradictory due to low power of studies,[17,18] and though several reviews or studies point to a mildly reduced antibody response in case of TNFi-treatment.[19-22] As a growing number of pregnant women with chronic inflammatory diseases receive TNFis, either alone or in combination with

prednisone or other immune-modulating drugs, knowledge whether such treatment may interfere with maternal Tdap vaccine responses and subsequent transplacental antibody transfer is urgently needed to adapt vaccination strategies for newborns born to mothers on TNFi-therapy.

In this pilot study, our co-primary objectives were to assess the effects of TNFi-treatment in patients with rheumatic diseases on maternal IgG antibody levels against pertussis in both infants around birth, and mothers three months after delivery. We performed external validation through the comparison of antibody levels in TNFi-exposed patients versus TNFi-unexposed patients and also in healthy maternal Tdap vaccinated women and their offspring from a historical comparison cohort.[11]

Methods

Study participants

Patients were derived from the PreCARA-study, which is a prospective cohort study on inflammatory rheumatic diseases before and during pregnancy.[23] Regarding the current study, pregnant patients were included as early as possible during pregnancy from January 2019 to February 2022, provided that they had received a Tdap vaccination during pregnancy. Tdap vaccinations were administered during the late-second or early-third trimester of pregnancy. All women and their offspring were followed until at least three months after delivery. Subscribed medication for rheumatic disease, including therapy with TNFis, was decided by a rheumatologist prior to inclusion in this study, based upon diagnosis and patients' medical conditions. Participants were divided into two groups, i.e. women on TNFis (used at any moment during pregnancy), and women not on TNFis. If patients were exposed to bDMARDS other than TNFis, they were excluded from the primary analysis, as the effects of non-TNFi bDMARDs on vaccination response in mothers were outside the scope of this study. These cases were assessed separately.

Venous blood samples were drawn from participants during their first trimester of pregnancy (i.e. before Tdap immunization) and approximately three months after delivery, along with a cord blood sample immediately after delivery. Samples were transported to the laboratory at room temperature and sera were stored at -80˚ Celsius awaiting laboratory analyses.

Data were compared with a historical comparator group of healthy pregnant women without rheumatic disease and their offspring, who participated in a maternal Tdap vaccination immunogenicity study between January 2014 and March 2016, as described previously.[11] All healthy pregnant women received

maternal Tdap vaccination between 30 and 33w gestational age (GA). In this cohort, blood samples were drawn right before immunization and within 48 hours after delivery by finger prick, along with a cord blood sample within the first few hours after birth.

For defining demographic variables; maternal age (years) was calculated as time interval between mothers' birth date and the date of delivery. Duration of rheumatic disease (years) was defined as the time since diagnosis until the date of delivery. Duration of pregnancy (weeks) was defined as time interval between first day of last menstruation period (LMP) and the date of delivery. Type of rheumatic disease was defined as the official diagnosis by a rheumatologist. Disease activity was determined by the Disease Activity Score with three variables: 28 swollen and tender joint count and C reactive protein (CRP) (DAS28CRP) and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score) in each trimester by a rheumatologist.

Laboratory analysis

Sera were analyzed in the laboratory of the National Institute of Public Health and the Environment (RIVM) as described previously.[24] In brief, IgG antibody concentrations against pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (Prn), diphtheria toxoid (Dt) and tetanus toxoid (TT) were determined by a bead-based fluorescent multiplex immunoassay using Luminex xMAP-map-Luminex technology.[24] In house reference serum and quality controls were used for pertussis antigens and sera were calibrated against the World Health Organization International Standard Pertussis Antiserum (serum reference 06/140). Native PT (Netherlands Vaccine Institute) was used. The lower limit of quantification was 0.21 international units (IU)/mL as restricted by the dilution series of the reference line. Sera from the comparator cohort had been stored and analyzed using the same procedures and in the same laboratory.[23]

Statistical analysis

This is a descriptive pilot study in a prospectively followed cohort of mother-infant-pairs who were divided in three groups; 1) patients on TNFis; 2) patients not on TNFis; 3) healthy reference cohort. Demographics and differences between these three groups were estimated using basic descriptive statistics analyzing two groups to another separately, e.g. by t-tests, chi-squared tests or non-parametric variants.

Absolute IgG antibody levels against the Tdap-vaccine antigens were log-transformed, assessed for following normal distributions and expressed in

geometric mean concentrations (GMCs). We compared pre-vaccination and post maternal Tdap GMCs in mothers three months after delivery between mother exposed and not exposed to TNFi. We could not compare these data with the healthy reference cohorts since considerable differences in timing of maternal Tdap vaccination and post-vaccination blood sampling existed between the current PreCARA-study cohort and historical healthy comparison cohort. Generalized estimating equation (GEE) models with an exchangeable correlation structure were used to adjust for any correlation between pairs of twins. For each of the Tdap-included antigens, crude GEE models were constructed. These models were constructed to calculate the p-values of GMC comparison between the groups before and after vaccination, and in cord sera. Regarding measurements in cord sera, we adjusted for GA at Tdap vaccination and pregnancy duration. For post-vaccination measurements, we adjusted for time interval between Tdap vaccination and the moment of postpartum blood sampling; this comparison was only made between two groups of PreCARA-cohort and not with the healthy participants.

Also by using GEE models, an indication of transplacental transfer rates was estimated as ratios between absolute fetal-to-maternal antibody levels (cord sera vs maternal post vaccination sera at three months after delivery) and compared between the two groups of rheumatic disease patients.

As corticosteroid therapy may also reduce antibody titres in response to vaccines,[25-27] a subgroup analysis was performed to assess the effects of combination therapy of TNFis with prednisone on GMCs in women with rheumatic disease.

All analyses were performed using R software, version 4.2.0.

Results

Demographics

In total, 66 pregnant patients with rheumatic diseases and a median age of 32.6 years (range 24-44) were enrolled in this study, of whom 46 were exposed and 20 unexposed to TNFis. Maternal Tdap vaccination was provided at a median of 27.6w GA (range: 20.0-36.1) in patients exposed to TNFis, 27.0 w GA (range: 19.3-34.0) in patients unexposed to TNFis and 31.2w GA (range: 29.8-33.0) in healthy controls. Based on the patients' medical history, 65 of total 66 patients had been vaccinated against pertussis diphtheria and tetanus as a child (almost exclusively whole cell pertussis vaccine since the neonatal acellular pertussis vaccine was introduced under the Dutch Immunization Program in 2001), and therefore maternal Tdap vaccination was considered a booster in these cases. Most frequently used

medication during pregnancy was certolizumab pegol (65%) in TNFi-exposed patients and hydroxychloroquine (56%) in TNFi-unexposed patients. Two patients received non-TNFi bDMARDs (rituximab and anakinra, n=1 each) and were not included in the primary analysis and analysed separately (see supplementary material Table S1).

The two groups of women with rheumatic disease either exposed or unexposed to TNFis had similar demographics, including age, pregnancy duration, GA at vaccination, and disease-related factors (Table 1). Healthy women were vaccinated later during pregnancy compared with TNFi-exposed and unexposed women (mean gestational week at vaccination: 31w, versus 28w and 27w respectively, $p<0.01$). Healthy women had also a significantly longer pregnancy duration than TNFi-exposed and a marginally longer pregnancy duration than TNFi-unexposed women (40, versus 39 and 39w, respectively) (Table 1).

GMCs before Tdap vaccination in pregnancy

GMCs against PT before vaccination were similar between patients exposed and unexposed to TNFis and healthy pregnant women (5.28 IU/mL, 95% CI 3.04-9.17 vs 4.25 IU/mL, 95% CI 2.12-8.53 vs 6.41 IU/mL, 95% CI 3.99-10.28, respectively). All other measured Tdap vaccine antigens also showed similar IgG levels except for Dt and Prn, for which the GMC in healthy women was lower than in TNFi-exposed patients ($p<0.05$) (Table 2, Figure 1, supplementary material Figure S1).

GMCs after Tdap vaccination in mothers with rheumatic disease

Three months after delivery following maternal Tdap vaccination, no significant differences in crude and adjusted analyses were observed in maternal GMCs against PT between TNFi-exposed vs unexposed patients (35.24 IU/mL, 95% CI 20.76-59.83 vs 50.6 IU/mL, 95% CI 26.49-96.62, respectively), though groups were small and 95% CI were large. Also for the other antigens, no significant differences in GMCs were observed (Table 2, Figure 1, supplementary material Figure S1).

Table 1. Patients' and healthy women's characteristics, stratified for use or no use of TNFis ever during pregnancy.

	Patients on TNFis; n=46	**P-value (TNFis vs no TNFis)**	**Patients not on TNFis; n=20**	**P-value (no TNFis vs healthy women)**	**Healthy women; n=53**	**P-value (TNFis vs healthy women)**
Age at delivery, years ±SD (range)	32.8±3.1 (25.1-40.1)	0.33	31.8±4.7 (24.6-43.9)	0.53	32.5±3.4 (23.7-42.7)	0.60
Time since disease diagnosis, years ±SD (range)	10.8±7.7 (0.5-30.0)	0.80	10.3±8.2 (1.0-31.0)	NA	NA	NA
Pregnancy duration at vaccination date, weeks ±SD [£] (range)	27.6±4.2 (20.0-36.1)	0.62	27.0±3.8 (19.3-34.0)	**<0.01**	31.2±0.8 (29.8-33.0)	**<0.01**
Pregnancy duration at delivery, weeks ±SD [€] (range)	38.7±1.8 (34.1-42.1)	0.40	39.1±1.9 (35.0-41.4)	0.11	39.8±1.5 (36.0-42.0)	**<0.01**
DAS28-CRP in 3rd trimester ±SD (range)	1.9±0.6 (1.3-5.3)	0.76	1.9±0.4 (1.4-2.7)	NA	NA	NA
BASDAI in 3rd trimester ±SD [$] (range)	3.2±1.6 (0.8-6.5)	0.43	2.4±1.1 (1.4-3.6)	NA	NA	NA
Diagnosis						
Rheumatoid Arthritis (RA)	13 (28%)	0.16	11 (55%)	NA	NA	NA
Juvenile Idiopathic Arthritis (JIA)	11 (24%)	0.22	3 (15%)	NA	NA	NA
Psoriatic Arthritis (PsA)	9 (19%)	0.25	2 (10%)	NA	NA	NA
Undifferentiated spondyloarthritis (SpA)	6 (13%)	0.28	0 (0%)	NA	NA	NA

Table 1. Continued.

	Patients on TNFis; n=46	P-value (TNFis vs no TNFis)	Patients not on TNFis; n=20	P-value (no TNFis vs healthy women)	Healthy women; n=53	P-value (TNFis vs healthy women)
Axial spondyloarthritis (axSpA)	4 (8%)	0.29	3 (15%)	NA	NA	NA
Other rheumatic disorders[@]	3 (6%)	0.30	1 (5%)	NA	NA	NA
Medication during pregnancy, any use[#]						
Hydroxychloroquine	21 (45%)	0.15	13 (65%)	NA	NA	NA
Sulfasalazine	17 (37%)	0.17	9 (45%)	NA	NA	NA
Prednisone	4 (9%)	0.20	4 (20%)	NA	NA	NA
Certolizumab-pegol	26 (56%)	NA	NA	NA	NA	NA
Etanercept	13 (28%)	NA	NA	NA	NA	NA
Adalimumab	6 (13%)	NA	NA	NA	NA	NA
Infliximab	6 (13%)	NA	NA	NA	NA	NA

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DAS28-CRP, 28-joint Disease Activity Score; NA: not applicable; SD, standard deviation. Vs. versus; * Values are given as mean ± SD or number (%) [$] Only in patients with SpA. @ including peripheral SpA (n=2) and oligo-arthritis (n=1) in exposed to TNFi group and polyarthritis (n=1) in TNFi-unexposed group. # Either alone or in combination with other medication. The sum of TNFis exceeds 45, because some patients switched from one TNFi to another during pregnancy. [€] Including one twin delivery in patients under TNFis and one in patients not on TNFis.

GMCs in cord sera

In cord sera from infants born to mothers on TNFis, GMCs against PT, Prn, FHA, Dt and TT were significantly lower compared with infants born to mothers who were unexposed to TNFis and lower compared with healthy women except for Dt (for PT: 35.94 IU/mL, 95% CI 20.68-62.45 vs 94.61 IU/mL, 95% CI 48.89-183.07 vs 125.12 IU/mL, 95% CI 90.75-172.50, respectively, table 2). TNFi-treatment resulted into a threefold reduction of anti-PT levels in cord blood compared with no treatment (adjusted GMC ratio 0.37, 95% CI 0.17-0.77) and a fourfold reduction compared with healthy controls (adjusted GMC ratio 0.25, 95% CI 0.13-0.49).

Between patients unexposed to TNFis and healthy women, cord serum GMCs were not significantly different in crude analyses, though after adjustments the p-value was significant for FHA (492.55 IU/mL, 95% CI 317.85-761.64 vs 321.19 IU/mL, 95% CI 248.11-415.79, respectively) (Table 2, Figure 1, supplementary material Figure S1).

IgG antibody transfer rates

Patients on TNFis showed significantly lower IgG antibody differences between cord blood levels and maternal anti-pertussis IgG levels at three months post-delivery, potentially suggesting lower transfer rates of all antigens compared with patients not on TNFis (mean fetal-to-maternal antibody ratios for PT: 1.33, 95% CI 1.05-1.60 in patients on TNFis vs 1.88, 95% CI 1.55-2.22 in patients not on TNFis). The single exception was Prn (mean ratio 1.18, 95% CI 0.91-1.45 in patients on TNFis vs 1.49, 95% CI 1.28-1.69 in patients not on TNFis, p=0.05), though with the same trend that failed to reach the level of significance. IgG antibody transfer rates tended to be higher in healthy women where ratios were between cord blood and levels in mothers immediately after delivery (for PT: 1.99, 95% CI 1.82-2.15), but direct comparisons with these women could not be made since maternal post-sera from patients were drawn at a different time-point than the healthy comparator group (Table 3).

Table 2. Geometric mean concentrations (IU/mL) of IgG antibodies with 95% confidence intervals in all study groups.

		TNFis vs no TNFis		
	GMCs of patients on TNFis	**Crude p-value**	**Adjusted p-value**	**Estimated GMC ratio (95% CI)**
Mothers before vaccination	**n=42**			
Anti-PT	5.28 (3.04-9.17)	0.54	NA	NA
Anti-FHA	17.33 (10.45-28.74)	0.95	NA	NA
Anti-Prn	17.93 (11.19-28.72)	0.85	NA	NA
Anti-Dt	0.10 (0.07-0.15)	0.58	NA	NA
Anti-TT	1.29 (0.93-1.78)	0.31	NA	NA
Mothers after vaccination	**n=43**			
Anti-PT	35.24 (20.76-59.83)	0.37	0.36	0.69 (0.31-1.52)
Anti-FHA	169.01 (126.34-226.09)	0.23	0.22	0.76 (0.49-1.18)
Anti-Prn	232.11 (147.17-366.08)	0.71	0.77	0.88 (0.37-2.08)
Anti-Dt	0.49 (0.35-0.69)	0.81	0.58	1.15 (0.70-1.88)
Anti-TT	5.01 (3.86-6.50)	0.79	0.96	1.01 (0.66-1.55)
Infants (umbilical cord)	**n=46**			
Anti-PT	35.94 (20.68-62.45)	**0.01**	**<0.01**	**0.37 (0.17-0.77)**
Anti-FHA	166.51 (112.46-246.55)	**<0.01**	**<0.01**	**0.32 (0.19-0.56)**
Anti-Prn	150.95 (83.92-271.49)	**<0.01**	**<0.01**	**0.23 (0.10-0.54)**
Anti-Dt	0.45 (0.29-0.69)	**0.03**	**0.03**	**0.54 (0.31-0.94)**
Anti-TT	4.55 (3.02-6.84)	**<0.01**	**<0.01**	**0.47 (0.30-0.74)**

Table 2. Continued.

		No TNFis vs healthy women		
	GMCs of patients not on TNFis	**Crude p-value**	**Adjusted p-value**	**Estimated GMC ratio (95% CI)**
Mothers before vaccination	**n=20**			
Anti-PT	4.25 (2.12-8.53)	0.30	NA	NA
Anti-FHA	16.97 (9.74-29.53)	0.09	NA	NA
Anti-Prn	19.49 (8.59-44.18)	0.07	NA	NA
Anti-Dt	0.09 (0.05-0.15)	0.06	NA	NA
Anti-TT	1.79 (0.98-3.28)	0.12	NA	NA
Mothers after vaccination	**n=18**			
Anti-PT	50.6 (26.49-96.62)	NA*	NA*	NA*
Anti-FHA	220.68 (151.67-321.11)	NA	NA	NA
Anti-Prn	272.07 (121.38-609.86)	NA	NA	NA
Anti-Dt	0.47 (0.32-0.69)	NA	NA	NA
Anti-TT	5.31 (3.65-7.72)	NA	NA	NA
Infants (umbilical cord)	**n=18**			
Anti-PT	94.61 (48.89-183.07)	0.43	0.30	0.68 (0.33-1.40)
Anti-FHA	492.55 (317.85-761.64)	0.05	**0.05**	**1.58 (1.01-2.48)**
Anti-Prn	607.16 (277.69-1327.5)	0.38	0.55	1.28 (0.57-2.86)
Anti-Dt	0.81 (0.53-1.24)	0.15	0.19	1.37 (0.85-2.19)
Anti-TT	9.43 (7.22-12.32)	0.06	0.20	1.24 (0.89-1.72)

Table 2. Continued.

		TNFis vs healthy women		
	GMCs of healthy women	**Crude p-value**	**Adjusted p-value**	**Estimated GMC ratio (95% CI)**
Mothers before vaccination	**n=53**			
Anti-PT	6.41 (3.99-10.28)	0.66	NA	NA
Anti-FHA	9.89 (6.76-14.46)	0.07	NA	NA
Anti-Prn	8.84 (5.77-13.54)	**0.02**	NA	NA
Anti-Dt	0.05 (0.03-0.07)	**<0.01**	NA	NA
Anti-TT	1.11 (0.87-1.42)	0.45	NA	NA
Mothers after vaccination	**n=53**			
Anti-PT	65.41 (47.56-89.96)	NA*	NA*	NA*
Anti-FHA	170.10 (132.61-218.18)	NA	NA	NA
Anti-Prn	261.51 (166.13-411.65)	NA	NA	NA
Anti-Dt	0.31 (0.23-0.43)	NA	NA	NA
Anti-TT	3.61 (3.00-4.35)	NA	NA	NA
Infants (umbilical cord)	**n=52**			
Anti-PT	125.12 (90.75-172.50)	**<0.01**	**<0.01**	**0.25 (0.13-0.49)**
Anti-FHA	321.19 (248.11-415.79)	**<0.01**	**<0.01**	**0.51 (0.32-0.81)**
Anti-Prn	435.41 (278.70-680.25)	**<0.01**	**<0.01**	**0.29 (0.14-0.59)**
Anti-Dt	0.59 (0.44-0.78)	0.29	0.24	0.73 (0.44-1.22)
Anti-TT	7.20 (5.95-8.71)	**0.04**	**0.02**	**0.58 (0.37-92)**

*As post-vaccination blood samples were obtained in different time points in Pre-CARA study and historical cohort of healthy pregnancies, no direct comparisons could be performed between GMCs after vaccination. GMC, geometric mean concentration; PT, pertussis toxin; FHA, filamentous hemagglutinin; Prn, pertactin, Dt, diphtheria toxoid, TT, tetanus toxoid; vs. versus.

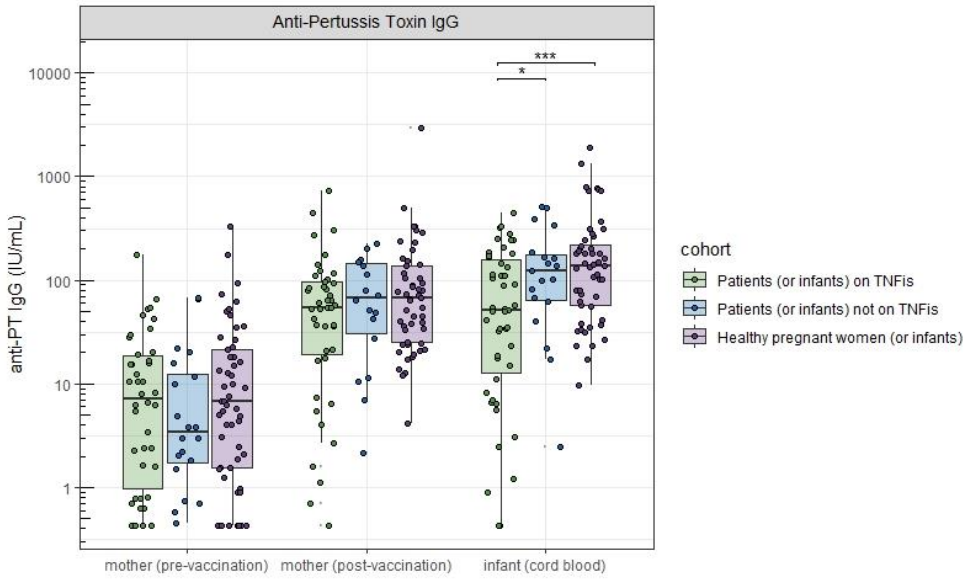

Figure 1. Anti-pertussis toxin (anti-PT IgG) concentrations (IU/mL) before and after vaccination and in cord sera, represented for women exposed or unexposed to TNFis, or healthy pregnant women, including their offspring. X-axis: type and time-point of blood sample draw. Y-axis: IgG antibody concentration against pertussis toxin (IU/mL). Significance *p<0.05, **p<0.01, ***p<0.001. TNFis, tumour necrosis factor alpha inhibitors.

Combined therapy with TNFi and prednisone

Subgroup analysis showed a lower GMC against PT after Tdap vaccination if patients were on combination therapy of prednisone and TNFis, compared with prednisone without TNFis, though with a very broad confidence interval (15.96 IU/mL, 95% CI 2.50-101.67, n=4 vs 105.14 IU/mL, 95% CI 36.08-306.32, n=4) (p=0.01) due to low power. A significant GMC difference was also observed in cord sera between women on combination therapy versus solely prednisone, again with a large confidence interval (41.84 IU/mL, 95% CI 9.07-192.91 vs 170.98 IU/mL, 95% CI 50.36-580.41, p=0.01). The few patients who used prednisone without TNFis (n=4) showed similar GMCs against PT in cord sera compared with healthy pregnant women (p=0.41) (supplementary material Figure S2).

Other biologicals

Among the two patients on non-TNFi bDMARDs, the patient on rituximab showed a relatively low IgG antibody concentration against PT in cord serum (1.57 IU/mL), but the patient on anakinra showed a concentration similar to that of healthy controls (152.4 IU/mL, see supplementary material Table S1).

Table 3. Mean fetal-to-maternal ratio of IgG antibodies with 95% confidence intervals in all study groups.

	Patients on TNFis	Patients not on TNFis	P-value (TNFis vs no TNFis)	Healthy women
Antigen	**n=43**	**n=18**		**n=52**
Anti-PT	1.33 (1.05-1.60)	1.88 (1.55-2.22)	**<0.01**	1.99 (1.82-2.15)
Anti-FHA	1.31 (1.02-1.61)	1.83 (1.50-2.17)	**0.01**	2.05 (1.85-2.25)
Anti-Prn	1.18 (0.91-1.45)	1.49 (1.28-1.69)	0.05	1.77 (1.62-1.93)
Anti-Dt	1.18 (0.96-1.41)	1.62 (1.43-1.82)	**<0.01**	1.88 (1.71-2.05)
Anti-TT	1.22 (1.00-1.45)	1.69 (1.39-1.99)	**<0.01**	2.09 (1.92-2.27)

PT, pertussis toxin; FHA, filamentous hemagglutinin; Prn, pertactin, Dt, diphtheria toxoid, TT, tetanus toxoid; vs. versus.

Discussion

To the best of our knowledge, this pilot study is the first to explore IgG antibody levels against pertussis-specific antigens following maternal Tdap vaccination in pregnant women on immune-modulating treatments with a focus in TNFi-treatment. Post-vaccination maternal serum GMCs against Tdap-specific antigens appeared not significantly affected by TNFis. In addition, we observed up to four-fold reduction in IgG antibody levels in infants' umbilical cord blood samples if mothers were under TNFi-therapy during pregnancy compared with mothers with no TNFi-therapy and healthy pregnant women.

Evidence on vaccine responses in patients on immune-modulating therapy is limited and contradictory.[28-32] Regarding coronavirus vaccination a meta-analysis of several studies has shown a substantial reduction in the humoral immune response to vaccination in non-pregnant patients under TNFi-therapy compared to healthy controls (odds ratio 0.94 [95% CI 0.84–0.98]).[33] Studies on other vaccines, e.g. pneumococcal and hepatitis A vaccines, also showed a reduced response in male and non-pregnant female patients under TNFi-treatment.[19,21] Nevertheless, regarding the booster vaccination after a complete childhood vaccination series, the majority of studies suggest that vaccines like Tdap vaccination, deliver sufficient vaccine (memory) responses in non-pregnant adults on immune-modulating treatments.[34-36] Our pilot study was in line with these findings of mostly sufficient memory responses under immune-modulating therapy, as we found no major reduction in IgG antibody responses after maternal Tdap vaccination in case of TNFi-treatment during pregnancy, though the power of our data was severely limited and a tendency to lower responses existed.

While in our study, the maternal Tdap vaccine response against several

vaccine-antigens appeared not significantly affected by treatment with TNFis, a small effect could not be excluded due to the small sample size. In addition, lower anti-pertussis antibody levels may have occurred in mothers post vaccination, since TNFis have been described to cause more rapid waning of IgG antibodies upon vaccination.[22,37] This may result in reduced transfer from mother to child. Noteworthy, the use of TNFis was associated with significantly lower GMCs in cord sera for all the Tdap-included antigens. In accordance, lower fetal-to-maternal antibody ratios were observed after treatment with TNFis compared with TNFi-unexposed women with rheumatic disease. This translates to reduced passive immunity against pertussis during first months after birth if the infant was born to mothers under TNFi.

We have investigated the effects of several confounding factors, which should also be assessed in future studies considering larger numbers of participants. In our study, healthy mothers were vaccinated later during pregnancy compared with patients with rheumatic disease. The optimal timing for maternal vaccination remains unknown, but a time interval of at least 6.0-7.5 weeks before delivery for both term and preterm born infants is postulated to result into enhanced antibody transfer.[38-40] In our study, the pregnancy duration of TNFi-exposed patients was somewhat shorter than in healthy women. Differences in cord blood GMCs still remained significant even after adjustment for time interval between Tdap vaccination and delivery. Therefore, it seems plausible that the lower GMCs in infants after maternal TNFi-exposure are related to the effect of the TNFis. In addition, apart from lower antibody responses another hypothesis is that TNFis may alter the function of the neonatal Fc receptor (FcRn), that is expressed by the syncytiotrophoblast, and that IgG antibody transfer across the placenta may be hampered by for example downregulation of FcRn. Competition between TNFis and IgG antibodies within this saturable process seems unlikely since the total amount of circulating IgG antibodies outnumbers the peripheral concentration of TNFis. We were unable to find studies on this topic and further research is needed.

Based on the results of our study, when pregnant patients receive a Tdap (booster) vaccination, and while their Tdap vaccine response may not be significantly affected, the ultimate levels in cord blood are less than expected. If this is the case for all the transfer of immunoglobulins G, it could be an alternative explanation why treatment with TNFis during pregnancy may be associated with slightly more infections in children (OR compared to the disease controlled group was 1.12, [95% CI = 1.00 to 1.27], p=0.05), in a meta-analysis by Barenbrug et al).[41] It has to be noted though that for pertussis, still no Correlate of Protection of IgG antibodies is available, and effectiveness and immunogenicity could not be directly

compared to another.

Although only a few patients in this study received TNFis and concomitant prednisone, they had significantly lower GMCs against PT in cord sera compared with the patients on prednisone without TNFis. To our knowledge, there is currently no available evidence on immunogenicity or efficacy of Tdap vaccination in patients with prednisone and TNFi combination therapy even outside of pregnancy. Further research with larger numbers is highly required for confirmation.

Reduced antibody responses have already been shown in non-pregnant adults following treatment with rituximab after inactivated vaccine use.[42] Within our study population, one patient was exposed to rituximab and had a reduced placental IgG antibody concentration of 1.57 IU/mL, which seems in line with previous research. Nevertheless, we could not further describe maternal antibody kinetics as no maternal post-vaccination samples were available from the mother exposed to rituximab.

A pilot study comes with limitations. Our findings are based on a small sample size in an observational study design, and may offer signals for potential immunogenic differences between patients and control groups, although it cannot account for many truly existing differences. External validation is recommended using larger numbers of subjects in each group within a parallel study design. Another limitation is the use of a historical comparator group with different time points of Tdap vaccination during pregnancy, timing of blood sampling (except for cord blood), and potential different exposure to endemic pertussis during coronavirus lockdown periods. Therefore, comparison of maternal post-vaccination GMCs between rheumatic disease patients and healthy pregnant women was not possible. Nevertheless, within the in-parallel included group of TNFi-exposed and unexposed patients, the same study protocol was followed, and therefore these two groups could be directly compared. A strength of the study is that, even though the study design is limited by comparison to data from a historical healthy control group, laboratory procedures were similar and analyses were performed by the same institute and research staff, and therefore any other bias than the factors that we could adjust for in the analyses would be negligible.

Recommendation for clinical practice

In the Netherlands after the introduction of maternal Tdap vaccination since 2019, the first infant pertussis vaccine is given around 3 months of age followed by a second vaccination at 5 months and then at 11 months. An extra pertussis vaccine is advised around six weeks to two months of age in cases with no maternal Tdap

vaccination, preterm infants, infants from immunodeficient mothers and infants born to mothers under TNFis.[43,44] Based on the results of our study and considering the serious consequences of pertussis in infants, particularly after preterm birth, the current approach in the Netherlands and the early start of primary series in the second month of life seems appropriate. Furthermore, an extra maternal booster during pregnancy could be considered, especially if mother is under combination TNF and prednisone therapy or in case of rituximab exposure.

Conclusion

Significantly lower cord serum GMCs against all Tdap-included antigens were observed if mothers were on TNFi-treatment during pregnancy compared to no TNFis or in healthy pregnant women. An early start with pertussis vaccination series at six weeks to two months of age is recommended in children born to mothers on TNFi-therapies during pregnancy. An alternative might be an extra Tdap vaccination during pregnancy though no data are yet available to support this strategy. The underlying mechanisms and clinical consequences for lower IgG antibody levels in infants remain unknown; further research is required.

Supplementary materials

Table S1. Pregnancies exposed to non-TNFi bDMARDs: Individual anti-pertussis IgG antibody levels before, after vaccination and in cord serum samples

Type of non-TNFi	Exposure length (weeks)	Concomitant medication	Anti-PT IgG level pre-vaccination (IU/mL)	Anti-PT IgG level post-vaccination (IU/mL)	Anti-PT IgG level cord serum (IU/mL)
Anakinra (n=1)	41	Prednisone	5.74	70.49	152.43
Rituximab (n=1)	2	Hydroxy-chloroquine, azathioprine, prednisone	NA	NA	1.57

bDMARDs, biological disease-modifying antirheumatic drugs; IU/mL, international units per mL; PT, pertussis toxin; TNFi, tumor necrosis factor inhibitors

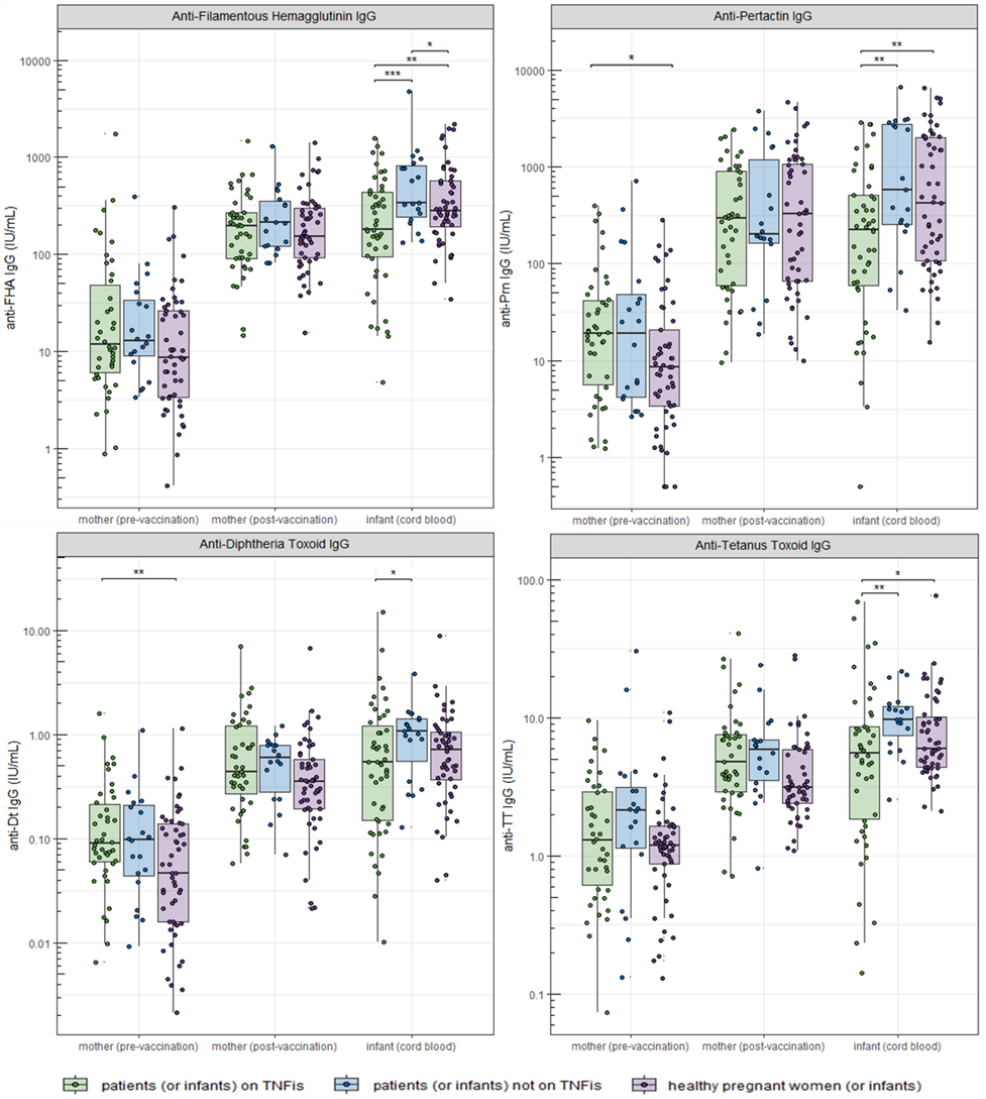

Figure S1. Anti-Filamentous hemagglutinin (FHA), Anti-Pertactin (Prn), Anti-Diphtheria toxoid (Dt) and Anti-Tetanus toxoid (TT) concentrations (IU/mL) before and after vaccination and in cord sera, represented for women exposed or unexposed to TNFis, or healthy pregnant women, including their offspring. X-axis: type and time-point of blood sample draw. Y-axis: IgG antibody concentration against the different antigens (IU/mL).

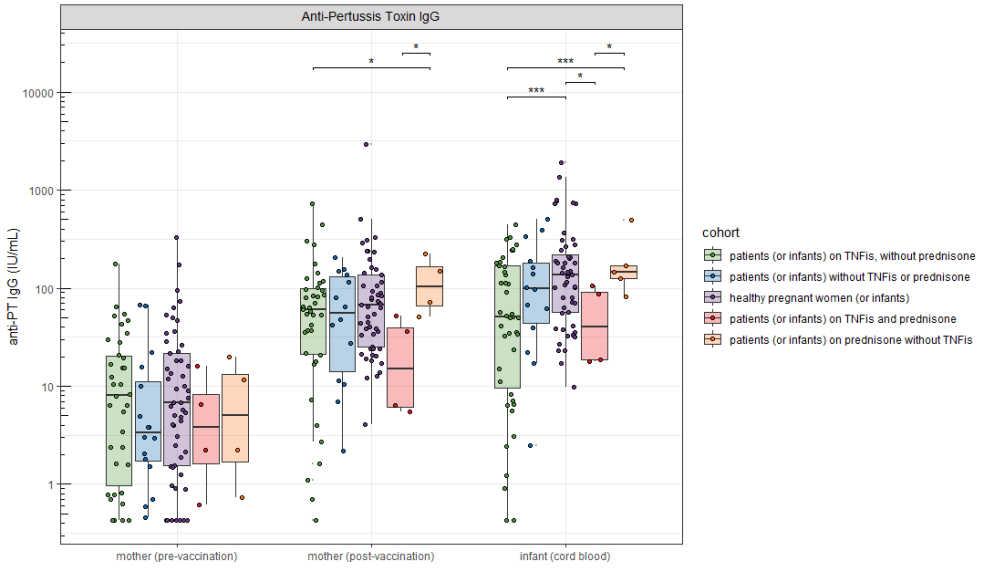

Figure S2. Anti-Pertussis toxin (anti-PT IgG) concentrations (IU/mL) before and after vaccination and in cord sera, represented for subgroup analysis based on use of TNFis and/or prednisone during pregnancy. X-axis: type and time-point of blood sample draw. Y-axis: IgG antibody concentration against pertussis toxin (IU/mL). Significance *p<0.05, **p<0.01, ***p<0.001.

References

1. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *The Lancet* 2014; **384**(9953): 1521-8.
2. van der Maas NAT, Mooi FR, de Greeff SC, Berbers GAM, Spaendonck MAEC-v, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? *Vaccine* 2013; **31**(41): 4541-7.
3. Yeung KHT, Duclos P, Nelson EAS, Hutubessy RCW. An update of the global burden of pertussis in children younger than 5 years: a modelling study. *The Lancet Infectious Diseases* 2017; **17**(9): 974-80.
4. de Greeff SC, Mooi FR, Westerhof A, et al. Pertussis disease burden in the household: how to protect young infants. *Clin Infect Dis* 2010; **50**(10): 1339-45.
5. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; **36**(5): 248-55.
6. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. *Arch Dis Child* 2018; **103**(3): 224-9.
7. Maertens K, Cabore RN, Huygen K, Hens N, Van Damme P, Leuridan E. Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. *Vaccine* 2016; **34**(1): 142-50.
8. Gotestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016; **75**(5): 795-810.
9. Bellido-Blasco J, Guiral-Rodrigo S, Míguez-Santiyán A, Salazar-Cifre A, González-Morán F. A case-control study to assess the effectiveness of pertussis vaccination during pregnancy on newborns, Valencian community, Spain, 1 March 2015 to 29 February 2016. *Euro Surveill* 2017; **22**(22).
10. Vaccine schedules in all countries in the EU/EEA. https://vaccine-schedule.ecdc.europa.eu/.
11. Barug D, Pronk I, van Houten MA, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. *Lancet Infect Dis* 2019; **19**(4): 392-401.
12. Krasselt M, Wagner U, Nguyen P, et al. Humoral and cellular response to COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases under real-life conditions. *Rheumatology (Oxford)* 2022; **61**(Si2): Si180-si8.
13. Nemeth D, Vago H, Tothfalusi L, et al. Factors influencing the SARS-CoV-2 infection and vaccination induced immune response in rheumatoid arthritis. *Front Immunol* 2022; **13**: 960001.
14. Yamaguchi Y, Nameki S, Kato Y, et al. Persistence of SARS-CoV-2 neutralizing antibodies and anti-Omicron IgG induced by BNT162b2 mRNA vaccine in patients with autoimmune inflammatory rheumatic disease: an explanatory study in Japan. *Lancet Reg Health West Pac* 2023; **32**: 100661.
15. Picchianti-Diamanti A, Aiello A, Laganà B, et al. ImmunosuppressiveTherapies Differently Modulate Humoral- and T-Cell-Specific Responses to COVID-19 mRNA Vaccine in Rheumatoid Arthritis Patients. *Front Immunol* 2021; **12**: 740249.
16. Mauro D, Ciancio A, Di Vico C, et al. Serological Response to BNT162b2 Anti-SARS-CoV-2 Vaccination in Patients with Inflammatory Rheumatic Diseases: Results From the RHEUVAX Cohort. *Front Immunol* 2022; **13**: 901055.
17. Arvas A. Vaccination in patients with immunosuppression. *Turk Pediatri Ars* 2014; **49**(3): 181-5.
18. Dezfoli S, Horton HA, Thepyasuwan N, et al. Combined Immunosuppression Impairs Immunogenicity to Tetanus and Pertussis Vaccination Among Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2015; **21**(8): 1754-60.
19. Silva CA, Aikawa NE, Bonfa E. Vaccinations in juvenile chronic inflammatory diseases: an update. *Nat Rev Rheumatol* 2013; **9**(9): 532-43.
20. Heijstek MW, Ott de Bruin LM, Bijl M, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis* 2011; **70**(10): 1704-12.
21. Farmaki E, Kanakoudi-Tsakalidou F, Spoulou V, et al. The effect of anti-TNF treatment on the immunogenicity and safety of the 7-valent conjugate pneumococcal vaccine in children with juvenile idiopathic arthritis. *Vaccine* 2010; **28**(31): 5109-13.

22. Ohm M, van Straalen JW, Zijlstra M, et al. Meningococcal ACWY conjugate vaccine immunogenicity and safety in adolescents with juvenile idiopathic arthritis and inflammatory bowel disease: A prospective observational cohort study. *Vaccine* 2023; **41**(25): 3782-9.
23. Smeele HTW, Röder E, Wintjes HM, Kranenburg-van Koppen LJC, Hazes JMW, Dolhain RJEM. Modern treatment approach results in low disease activity in 90% of pregnant rheumatoid arthritis patients: the PreCARA study. *Annals of the Rheumatic Diseases* 2021; **80**(7): 859-64.
24. van Gageldonk PG, van Schaijk FG, van der Klis FR, Berbers GA. Development and validation of a multiplex immunoassay for the simultaneous determination of serum antibodies to Bordetella pertussis, diphtheria and tetanus. *J Immunol Methods* 2008; **335**(1-2): 79-89.
25. Battafarano DF, Battafarano NJ, Larsen L, et al. Antigen-specific antibody responses in lupus patients following immunization. *Arthritis Rheum* 1998; **41**(10): 1828-34.
26. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clinical infectious diseases* 2014; **58**(3): e44-e100.
27. Robinson MJ, Heal C, Gardener E, Powell P, Sims DG. Antibody response to diphtheria-tetanus-pertussis immunization in preterm infants who receive dexamethasone for chronic lung disease. *Pediatrics* 2004; **113**(4): 733-7.
28. Keller M, Pittet LF, Zimmermann P. Immunogenicity and safety of routine vaccines in children and adolescents with rheumatic diseases on immunosuppressive treatment - a systematic review. *Eur J Pediatr* 2022; **181**(4): 1329-62.
29. van Assen S, Elkayam O, Agmon-Levin N, et al. Vaccination in adult patients with auto-immune inflammatory rheumatic diseases: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for vaccination in adult patients with auto-immune inflammatory rheumatic diseases. *Autoimmun Rev* 2011; **10**(6): 341-52.
30. Buhler S, Eperon G, Ribi C, et al. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. *Swiss Med Wkly* 2015; **145**: w14159.
31. Ling J, Koren G. Challenges in vaccinating infants born to mothers taking immunoglobulin biologicals during pregnancy. *Expert Rev Vaccines* 2016; **15**(2): 239-56.
32. McMahan ZH, Bingham CO, 3rd. Effects of biological and non-biological immunomodulatory therapies on the immunogenicity of vaccines in patients with rheumatic diseases. *Arthritis Res Ther* 2014; **16**(6): 506.
33. Sood A, Tran M, Murthy V, Gonzalez E. Immunogenicity and Safety of SARS-CoV-2 Vaccination in Patients With Rheumatic Diseases: A Systematic Review and Meta-analysis. *J Clin Rheumatol* 2022; **28**(8): 381-9.
34. Appels R, adviseur Rijksvaccinatieprogramma M, Betjes RDM, et al. Vaccinatie bij chronisch inflammatoire aandoeningen Handleiding.
35. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020; **79**(1): 39-52.
36. Rondaan C, Furer V, Heijstek MW, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. *RMD Open* 2019; **5**(2): e001035.
37. Stoof SP, Heijstek MW, Sijssens KM, et al. Kinetics of the long-term antibody response after meningococcal C vaccination in patients with juvenile idiopathic arthritis: a retrospective cohort study. *Ann Rheum Dis* 2014; **73**(4): 728-34.
38. Ciobanu AM, Dumitru AE, Gica N, Botezatu R, Peltecu G, Panaitescu AM. Benefits and Risks of IgG Transplacental Transfer. *Diagnostics (Basel)* 2020; **10**(8).
39. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *Clin Infect Dis* 2016; **62**(7): 829-36.
40. Gomme J, Wanlapakorn N, Ha HTT, Leuridan E, Herzog SA, Maertens K. The Impact of Timing of Pertussis Vaccination During Pregnancy on Infant Antibody Levels at Birth: A Multi-Country Analysis. *Front Immunol* 2022; **13**: 913922.
41. Barenbrug L, Groen MT, Hoentjen F, et al. Pregnancy and neonatal outcomes in women with immune mediated inflammatory diseases exposed to anti-tumor necrosis factor-α during pregnancy: A systemic review and meta-analysis. *J Autoimmun* 2021; **122**: 102676.
42. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum* 2010; **62**(1): 75-81.

43. Niemansburg S. Kinkhoestvaccinatie zwangeren ter bescherming van zuigeling. Springer; 2017.
44. van der Maas NAT, Ruijs WLM, Rots N, de Melker HE. Bescherming van de pasgeborene tegen kinkhoest; wat is de optimale strategie? *Tijdschrift voor Infectieziekten* 2017; **12**: 196-202.

CHAPTER 6

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 20-24w 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 30-33w 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 (≥38.0˚C). 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.

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 1990s 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.

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.

Methods

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).

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 0.5mL intramuscular injection in the upper arm deltoid muscle. In case participants were ill or had fever (≥38.0˚C), administration was postponed until recovery.

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˚C, moderate-grade 39.0-39.9˚C, high-grade 40.0-40.9˚C and hyperpyrexia ≥41.0˚C) 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˚C); 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 30-33 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”.

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 minutes, admission to a neonatal intensive care unit ward.

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.

Results

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.

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%) (Figure 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 (Figure 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.

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

	Between 20-24w GA vaccinated study population (n=723)[a]	Between 30-33w 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

[a] Demographic 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.

Systemic adverse events

After vaccination, 460 participants (63.6%) reported at least one systemic AE (Figure 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) (Figure 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 Figure 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) (Figure 2) were more frequently reported.

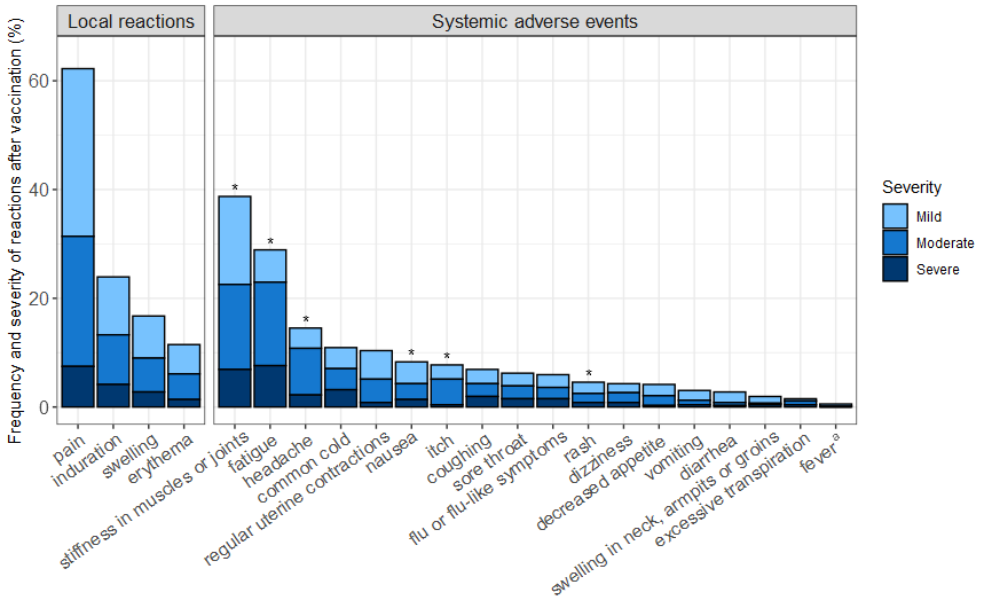

Figure 1. Frequency and self-reported severity (%) of local reactions at the injection site and systemic AEs within 7 days after maternal Tdap vaccination. [a] For fever, categories were low-grade (mild-blue), moderate-grade (moderate-blue), high-grade (NA), and hyperpyrexia (NA) (see main text for corresponding temperatures) * significant systemic symptoms that were more observed post-Tdap vaccination ($p<0.05$).

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

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 30-33 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 20-24 weeks GA compared to 30-33 weeks GA (Table 2).

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).

	Week before vaccination		Week after vaccination			
	% (95% CI)	Median duration, days (IQR)	% (95% CI)	Median onset time since vaccination, days (IQR)	Median duration, days (IQR)	OR[a] (95% CI)
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)

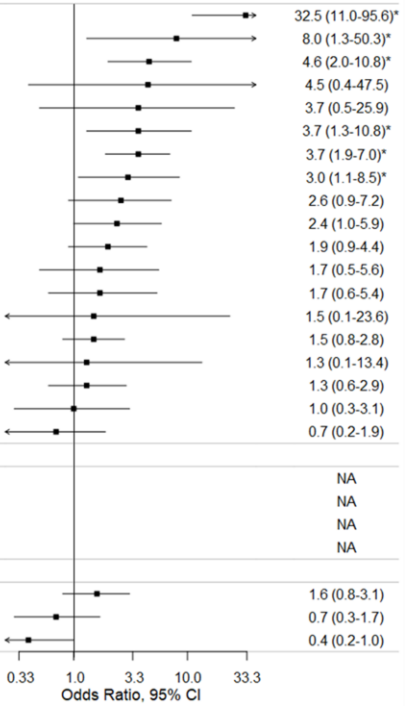

Figure 2. Occurrence of systemic adverse events and local reactions within 7 days before and/or after maternal Tdap vaccination. CI, confidence interval; IQR, inter-quartile range; OR, odds ratio. [a]Odds ratios for systemic events and other variables were computed by binary generalized mixed models 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 $p<0.05$.

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

	Between 20-24w GA vaccinated study population (n=723)	Between 30-33w 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 (≥38.0˚C)	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.[5] [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 minutes, 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.

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 20-24 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 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.

References

1. Kandeil W, van den Ende C, Bunge EM, Jenkins VA, Ceregido MA, Guignard A. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. *Expert Rev Vaccines* 2020; **19**(7): 621-38.
2. Healy CM, Rench MA, Swaim LS, et al. Association Between Third-Trimester Tdap Immunization and Neonatal Pertussis Antibody Concentration. *JAMA* 2018; **320**(14): 1464-70.
3. Edwards K, Freeman DM. Adolescent and adult pertussis: disease burden and prevention. *Curr Opin Pediatr* 2006; **18**(1): 77-80.
4. Rothstein E, Edwards K. Health burden of pertussis in adolescents and adults. *Pediatr Infect Dis J* 2005; **24**(5 Suppl): S44-7.
5. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014; **384**(9953): 1521-8.
6. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. *Clin Infect Dis* 2017; **64**(1): 3-8.
7. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. *Emerg Infect Dis* 2000; **6**(4): 348-57.
8. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; **36**(5): 248-55.
9. Vygen-Bonnet S, Hellenbrand W, Garbe E, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. *BMC Infect Dis* 2020; **20**(1): 136.
10. Dabrera G, Amirthalingam G, Andrews N, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. *Clin Infect Dis* 2015; **60**(3): 333-7.
11. Amirthalingam G, Campbell H, Ribeiro S, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. *Clin Infect Dis* 2016; **63**(suppl 4): S236-S43.
12. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. *Pediatrics* 2017; **139**(5).
13. McMillan M, Clarke M, Parrella A, Fell DB, Amirthalingam G, Marshall HS. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. *Obstet Gynecol* 2017; **129**(3): 560-73.
14. Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA* 2014; **311**(17): 1760-9.
15. Fortner KB, Swamy GK, Broder KR, et al. Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women. *Vaccine* 2018; **36**(42): 6354-60.
16. Regan AK, Tracey LE, Blyth CC, Richmond PC, Effler PV. A prospective cohort study assessing the reactogenicity of pertussis and influenza vaccines administered during pregnancy. *Vaccine* 2016; **34**(20): 2299-304.
17. Sukumaran L, McCarthy NL, Kharbanda EO, et al. Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes Among Pregnant Women With Prior Tetanus-Containing Immunizations. *JAMA* 2015; **314**(15): 1581-7.
18. Barug D, Pronk I, van Houten MA, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. *Lancet Infect Dis* 2019; **19**(4): 392-401.
19. Immink MM, Bekker MN, de Melker HE, Rots NY, Sanders EAM, van der Maas NAT. Study protocol of the PIMPI-project, a cohort study on acceptance, tolerability and immunogenicity of second trimester maternal pertussis immunization in relation to term and preterm infants. *BMC Infect Dis* 2021; **21**(1): 897.
20. Perined. The Dutch Perinatal Registry. www.perined.nl.
21. Boostrix ®, Official Product Information. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Boostrix/pdf/BOOSTRIX.PDF.

22. Hoftiezer L, Hukkelhoven CW, Hogeveen M, Straatman HM, van Lingen RA. Defining small-for-gestational-age: prescriptive versus descriptive birthweight standards. *Eur J Pediatr* 2016; **175**(8): 1047-57.
23. Wanlapakorn N, Maertens K, Chaithongwongwatthana S, et al. Assessing the reactogenicity of Tdap vaccine administered during pregnancy and antibodies to Bordetella pertussis antigens in maternal and cord sera of Thai women. *Vaccine* 2018; **36**(11): 1453-9.
24. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. *JAMA* 2014; **312**(18): 1897-904.
25. Peristat. 2021. https://www.peristat.nl/.

CHAPTER 7

Background incidence rates of adverse pregnancy outcomes in the Netherlands; data of 2006-2018

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Abstract

Objective

Maternal vaccination is an effective and safe intervention to protect newborns against infectious diseases shortly after birth. We assessed background rates of adverse pregnancy outcomes before the implementation of a maternal pertussis immunisation programme in the Netherlands, to put into perspective the safety concerns about such outcomes following immunisation.

Study Design

In this retrospective cross-sectional study, annual numbers of pregnancy outcomes derived from the Dutch Perinatal Registry were used to calculate incidence rates per 10,000 in the 2006-2018 period. Births of ≥500g birth weight and ≥24+0w gestational age were included. Trends with moving-average-lines over the past 3 years were plotted, with 95% confidence interval.

Results

From 2006 through 2018, yearly numbers of pregnancies ranged between 158,868-175,710. Numbers of newborns ranged between 161,307-178,874, of whom 160,838-178,177 were live-born. Most outcomes were stable over time. Between 2006-2011, occurrence of labour induction increased by 68%, and postpartum hemorrhage increased by 25%. Both stabilised from 2011 onwards. Perinatal mortality up to day 7 or 28 postpartum decreased by 38% and 37%, respectively. Occurrence of low Apgar score among preterm infants born before 37+0w gestational age and among term infants increased by 19% and 27%, respectively.

Conclusion

Our study on background incidences showed notable increases over time in occurrence of labour induction, postpartum hemorrhage and low Apgar score, while showing a considerable decrease in overall perinatal mortality. These findings should be considered when interpreting data on adverse events occurring since the maternal pertussis immunisation programme was implemented.

Background

Infants too young to be vaccinated depend on maternal antibodies for protection against infectious diseases, such as pertussis. These infants are at increased risk of severe pertussis complications, leading to hospitalisation and sometimes even death.[1-4] During pregnancy, IgG-antibodies, produced in the mother after infection or immunisation, are then transferred to the fetus through the placenta. Recent studies show that an early-second-trimester tetanus, diphtheria and acellular pertussis (Tdap) vaccination significantly increases pertussis-specific antibodies in term and preterm infants compared to third-trimester vaccination.[5,6] Therefore, an increasing number of countries now recommend Tdap immunisation earlier in gestation. In the Netherlands since December 2019, the National Immunisation Programme (NIP) offers Tdap vaccination to all pregnant women of at least 22 weeks (w) gestational age (GA).

Studies in (non-pregnant) women have shown that injection site reactions and systemic reactions like headache and fatigue were related to Tdap vaccination.[7-9] Its use during pregnancy has been extensively studied and is considered safe, without increased risk of a wide range of adverse pregnancy outcomes.[10-13] Some non-randomised studies reported a small increased risk of chorioamnionitis in women who were immunised against pertussis, but found no increased frequency for clinically relevant sequelae, e.g. earlier onset of labour, resulting in preterm delivery.[11,14-16]

Various adverse pregnancy outcomes, such as (pre-)eclampsia, preterm delivery, or low birth weight, emerging shortly after Tdap immunisation, could be considered an adverse reaction to the vaccine. Therefore, despite the favorable safety profile of the Tdap vaccine, implementation of such maternal immunisation programmes can raise public safety concerns. To distinguish legitimate safety concerns from coincidental events following immunisation, we assessed background rates of adverse pregnancy outcomes at maternal and neonatal level prior to the 2019 implementation of a maternal Tdap immunisation programme in the Netherlands. Assessing these background rates is important for evaluating the safety of the Tdap vaccination since its implementation and evaluating future maternal immunisation strategies.

Methods

Data source

We used routinely collected data from the Dutch Perinatal Registry (DPR; www.perined.nl) to extract information about adverse pregnancy outcomes from 2006 through 2018. The DPR database contains the anonymous and interconnected

data of national registries of four professional organisations that provide perinatal care in the Netherlands, i.e. midwives, general practitioners, gynecologists, and pediatricians. It contains prospectively obtained population-based data on pregnancies and the care provided for newborns, e.g. interventions, referrals, deliveries and admissions, of approximately 98% of all deliveries in The Netherlands.[17]

Study population and setting

Our study population consisted of 98% of all pregnant women and their infants as recorded by DPR from 2006 through 2018. Births of ≥500 g birth weight and ≥24+0 w GA were included. All data obtained from the DPR database were extracted from individual medical records and rendered anonymous, taking the European privacy policy into account. Therefore, medical ethical approval and individual informed consent for participation were not necessary.[18]

Outcome measures

Box 1 shows the outcomes we selected for this study. Case definitions are described in Supplementary Table 1. Variables requiring an additional explanation are described below.

Box 1. Adverse pregnancy outcomes to be possibly assigned to the Tdap vaccination

Maternal outcomes

maternal mortality; placental abruption; hypertension; (pre-)eclampsia; rupture of membranes ≥24h pre-labour; labour induction; instrumental delivery and caesarian section (i.e. vacuum delivery, forceps delivery, caesarian section); uterine rupture; postpartum hemorrhage.

Neonatal outcomes

stillbirth; neonatal mortality; perinatal mortality; prematurity <28+0w and <37+0w GA; small (<10^{th} percentile) and large (>90^{th} percentile) for GA (SGA and LGA); severe congenital malformations; low Apgar score (<7 at 5 min after birth); resuscitation; neonatal hospital admission; level III Neonatal Intensive Care Unit (NICU) admission; idiopathic respiratory distress syndrome (IRDS), neonatal sepsis; neonatal infections, including sepsis; mean difference in days between hospital discharge date and expected delivery date.

Additional explanation of outcomes

Pre-eclampsia and eclampsia were combined because separate data were not available. Postpartum hemorrhage was defined as ≥1000mL blood loss in the first

24h after delivery.

Since we only included cases of ≥24+0w GA, stillbirth was defined as death in the period between 24+0w GA and birth. Likewise, neonatal mortality was defined as death in the period from birth until 28 days (d) after birth. Perinatal mortality was calculated for infants until 7d or 28d after birth.

Small for gestational age (SGA) and large for gestational age (LGA) were determined using Hoftiezer charts, in which percentiles of birth weight versus GA have been calculated with SGA and LGA defined as <10th percentile and >90th percentile, respectively.[19]

We decided to restrict neonatal hospital admissions to infants who were hospitalised due to a medical indication. Infants born after a caesarean section usually remain hospitalised for a short time, but this reflects standard care and is not in itself an adverse outcome.

Idiopathic respiratory distress syndrome (IRDS) was determined for preterms only, because its prevalence in term infants is extremely low.

Mean length of hospital stay cannot be used as an adverse pregnancy outcome, because it is directly affected by GA. Therefore, the mean difference in days between hospital discharge date and the expected delivery date is used as a proxy for the need of hospitalisation in preterms with divergent lengths of GA.

Outcome measures directly associated with GA, e.g. low Apgar score at 5 min, were (also) analyzed in categories of prematurity; extreme preterms (<28+0w GA), all preterms (<37+0w GA) and infants born at term (≥ 37+0w GA).

Because in the Netherlands the maternal Tdap vaccination can be administered from 22+0w GA onwards, we additionally specified incidence rates (IR) of stillbirth, neonatal mortality and perinatal mortality for all cases between 22+0w GA and 23+6w GA.

Statistical analysis

To calculate IRs per 10,000 from 2006 through 2018, we used annual numbers of pregnancy outcomes, divided by the total number of pregnancies or births each year for maternal and infant outcomes, respectively. Additional moving averages of the past 3 years were plotted from 2008 onwards, containing a 95% confidence interval (CI). Data retrieval was performed using R-software version 1.2.5042.

Results

From 2006 through 2018, yearly numbers of pregnancies ranged between 158,868 and 175,710. Yearly numbers of newborns ranged between 161,307 and 178,874, of whom 160,838 to 178,177 were live-born. Table 1 shows IRs of included

maternal and infant outcomes per 10,000 from 2006 through 2018.

Table 1. incidence rates per 10,000 of adverse pregnancy and birth outcomes for 2006-2018

	Mean incidence rate per 10,000 (median; range)
Maternal level	
Maternal mortality	0.4 (0.4; 0.2-0.7)
Placental abruption	17 (17; 15-19)
Hypertension	599 (604; 535-663)
(Pre-)eclampsia	34 (29; 22-51)
Rupture of membranes ≥24h pre-labour	658 (658; 613-709)
Labour induction	1853 (2028; 1228-2148)
Uterine rupture	0.9 (0.8; 0.5-1.4)
Instrumental delivery and caesarean section	2463 (2495; 2194-2672)
Vacuum delivery	891 (908; 695-1012)
Forceps delivery	28 (27; 11-5)
Caesarean section	1578 (1596; 1470-1679)
Postpartum hemorrhage (≥1000mL)	609 (629; 505-646)
Neonatal level	
Stillbirth	36 (35; 27-51)
Neonatal mortality (up to 28d postpartum)	22 (22; 17-28)
Perinatal mortality (up to 7d postpartum)	53 (50; 43-73)
Perinatal mortality (up to 28d postpartum)	59 (56; 47-79)[*]
Prematurity <28+0w Gestational age	38 (38; 35-40)
Prematurity <37+0w Gestational age	735 (739; 679-782)
Small for gestational age (<10th percentile of Hoftiezer)	1085 (1073; 1035-1176)
Large for gestational age (>90th percentile of Hoftiezer)	1030 (1020; 968-1114)
Severe congenital malformations[a]	24 (25; 16-29)
Low Apgar score (<7 at 5 min)	183 (187; 162-203)
Resuscitation	284 (286; 210-348)
Neonatal hospital admission[b]	1683 (1683; 1186-2209)
Neonatal intensive care unit admission	355 (385; 207-467)

[a.] Tract specific and multiple and syndromic congenital malformations combined (supplement).

[b.] Excluding admission after caesarean section without other diagnosis.

[*.] Perinatal mortality is the sum of stillbirth and neonatal mortality. Mean numbers did not add up correctly due to rounding.

Figures 1 and 2 show time trends for all maternal and neonatal outcomes.

IRs of labour induction increased by 68% between 2006 and 2011 (1228 to 2067

per 10,000) (Figure 1). IRs stabilised afterwards, ranging between 2022-2148 per 10,000. Sub-analyses showed that the mean GA between 2006 and 2011 decreased by three days among women who gave birth after labour induction at ≥40+0w GA (from 41+4w GA in 2006 to 41+1w GA in 2011). IRs of postpartum hemorrhage increased by 25% (504 to 631 per 10,000) in the same period and stabilised from 2011 through 2018, ranging between 611-646 per 10,000. Overall, the IRs of instrumental delivery and caesarian section remained stable over the observed period, with caesarian section fluctuating between 1470 and 1507 per 10,000, whereas vacuum delivery and forceps delivery decreased, the former from 980 to 695 per 10,000 and the latter from 55 to 12 per 10,000.

IRs of LGA fluctuated, with a maximum of 1114 per 10,000 in 2008 and a minimum of 968 per 10,000 in 2015 (Figure 2). IRs of SGA decreased by 11% (1176 to 1047 per 10,000) between 2006 and 2018. IRs of stillbirth decreased by 43% (51 to 29 per 10,000). IRs of neonatal mortality decreased by 25% (28 to 21 per 10,000). As a result, IRs of perinatal mortality decreased by 38% (73 to 45 per 10,000) up to 7d postpartum and 37% (79 to 50 per 10,000) up to 28d postpartum. IRs of severe congenital malformations decreased by 45% (29 to 16 per 10,000) from 2006 through 2018. IRs for neonatal hospital admissions and NICU admissions showed fluctuations over the observed period, ranging between 1186-2209 per 10,000 for neonatal hospital admissions and 207-467 per 10,000 for NICU admissions.

The number of births ≥22+0w and ≤23+6w GA ranged by 25 to 30 per 10,000 over the 2006-2018 period. Among these infants, perinatal mortality was nearly 100% at all times over the observed period; 62-70% died during pregnancy and 29-36% died shortly after birth.

IRs of prematurity slightly decreased from 2006 through 2018 in both preterm categories, <28+0w GA and <37+0w GA, with a decrease of 7.7% (39 to 36 per 10,000) for those <28+0w GA compared to 9.4% (766 to 679 per 10,000) for those <37+0w GA. IRs of low Apgar score increased by 19% (878 to 1044 per 10,000) among preterms <37+0w GA compared to 27% (108 to 137 per 10,000) among term infants (Table 2). Low Apgar score was most prevalent among preterm infants <28+0w GA and fluctuated over the entire study period with a range of 4592-5631 per 10,000. Likewise, IRDS was most prevalent among preterms <28+0w GA. Between 2006 and 2007, we saw an increase in IRDS of 69% (3521 to 5952 per 10,000) in preterms <28w GA, which gradually decreased by 25% between 2007 and 2018 (5952 to 4492 per 10,000). The mean number of days between hospital discharge date and expected delivery date for all preterm infants ranged between 22 and 26.

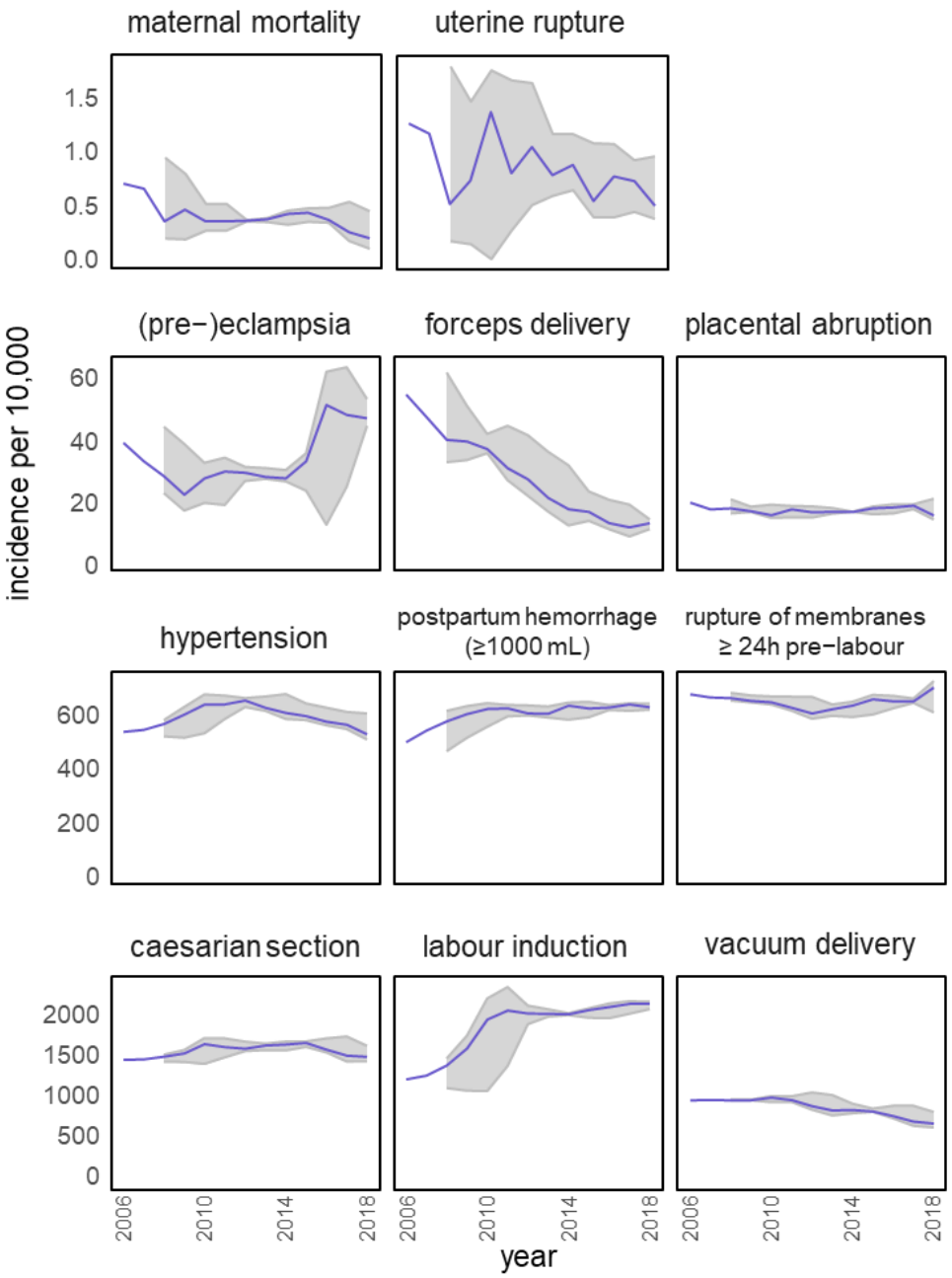

Figure 1. Trends per 10,000 of adverse outcomes at maternal level for 2006-2018.
The 95% confidence interval was derived from the moving average trend calculated over the previous 3 years.

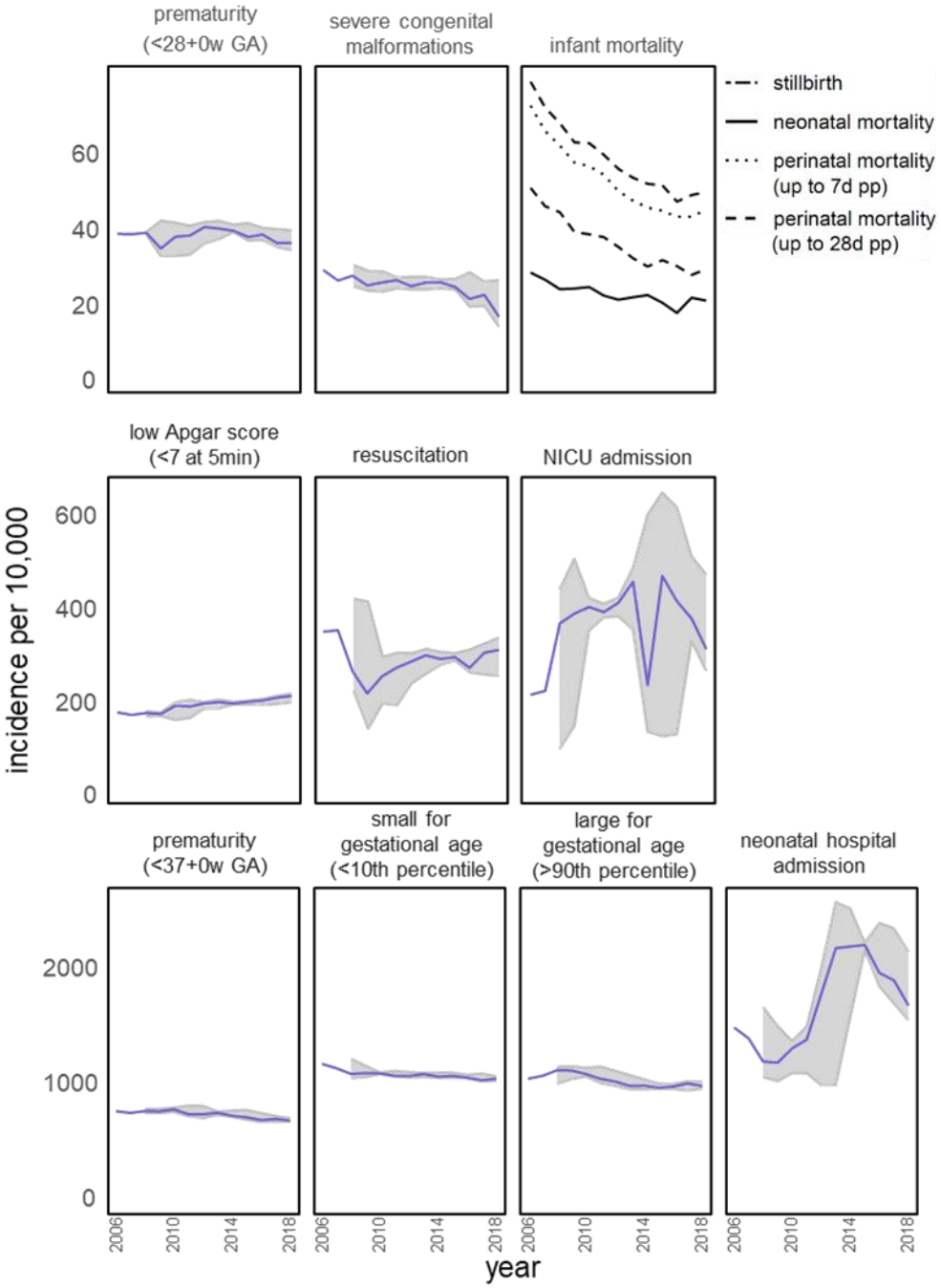

Figure 2. Trends per 10,000 of adverse outcomes at neonatal level for 2006-2018.
The 95% confidence interval was derived from the moving average trend calculated over the previous 3 years.

Discussion

The results of the present study show that over 13 years (2006-2018), the occurrence of most pregnancy outcomes remained rather stable in the Netherlands, with no substantial changes over time. However, notable changes included increases in the occurrence of labour induction, postpartum hemorrhage, and low Apgar score, whereas a decrease was observed in overall perinatal mortality.

Changes in IRs of pregnancy outcomes may be partially explained by changes in medical care. Since 2007, the guidelines for post-term pregnancies allowed the possibility of labour induction earlier in gestation: after 41+0w GA instead of after 42+0w GA.[20] Until 2011, we observed an increase in occurrence of labour induction. In the same period, we observed an increase in occurrence of postpartum hemorrhage. Despite the simultaneously occurring increases, there is no evidence to suggest an association between labour induction and postpartum hemorrhage.[21,22] Since 2011, both have stabilised, and therefore the most recent IRs reflect the current background incidence and are not expected to increase or decrease in the near future.

The decreased occurrence of stillbirth over the observed period led to a decrease in overall perinatal mortality, i.e. the sum of fetal (stillbirth) and neonatal mortality. The decrease in stillbirths may result in an increased number of live-born but more vulnerable infants, with a higher risk of neonatal mortality. This might partially explain the smaller decrease in neonatal mortality relative to the larger decrease in occurrence of stillbirth. The same mechanism holds for low Apgar score. Fewer fetal deaths, and therefore a higher percentage of more vulnerable infants might have partially led to the small increase in occurrence of low Apgar score over the observed period. The decreased occurrence of severe congenital malformations might be partially explained by the introduction of the 20-week fetal anomaly scan in 2007, possibly resulting into more terminations of pregnancy before 24+0w GA.[23] For IRDS among preterms <28w GA, we observed an increase from 2006 to 2007. Notably, in 2006, the Dutch guidelines for active treatment of extremely preterm neonates advised lowering the GA threshold for active intervention from 26+0 to 25+0w GA.[24]

Perinatal mortality for infants born between 22+0w GA and 23+6w GA was investigated to give context to the adverse events that occurred after maternal Tdap vaccination was administered, in the first weeks after the earliest opportunity of Tdap vaccination within the NIP. We found no substantial changes in IRs over the entire observed period. However, in 2010, the definition of viability changed to a threshold of at least 24+0w GA. This might have introduced incompleteness into

the DPR data, which could have affected our findings in either direction.

Chorioamnionitis is not registered in the DPR. Studies suggesting that Tdap immunisation increases the risk of chorioamnionitis have not reported associations with other maternal or perinatal adverse outcomes.[11,14,15] The clinical relevance of chorioamnionitis is unclear. A diagnosis of chorioamnionitis is solely based on clinical criteria, i.e. fever and two of the following: uterine tenderness or maternal or fetal tachycardia or foul/purulent amniotic fluid. Therefore, clinical chorioamnionitis is diagnosed with variable sensitivity and low specificity.[25] Sequelae to this diagnosis should be more extensively studied in relation to Tdap immunisation.

Two other studies described adverse outcomes in pregnancy associated with maternal vaccination safety in a national population setting. An observational study in New Zealand reported mean incidences of 4.7% for preterm delivery (defined as <37+0w GA), 8.7% for postpartum hemorrhage, 7.5% for rupture of membranes ≥24h pre-labour and 0.4% for placental abruption,[26] which were all similar to our results, i.e. 7.4%, 6.1%, 6.6% and 0.2%, respectively. A survey among pregnant active duty United States military women reported results for adverse outcomes that included a mean incidence of 7.7% for preterm delivery (<37+0w GA), which was similar to our finding of 7.4%.[27]

A major strength of our study is that the DPR provides medical information about 98% of all pregnancies and births in the Netherlands and is therefore highly representative of the Dutch population. The currently assessed background rates will be used to guide safety surveillance of the maternal pertussis vaccination programme. The data can also be used as information source for strategies to implement other types of maternal immunisation in the future, e.g. maternal vaccination targeting respiratory syncytial virus or group B streptococcus.

Over the years under study, there might have been some changes in the completeness of the registration into DPR. Between 2006 and 2015, we saw an increase in neonatal wards providing data to DPR. This might have had impact on IRs of neonatal hospital admission between those years. Additionally, data of upcoming external neonatal cardiology and neonatal oncology departments in the Netherlands were not incorporated in the DPR database, thereby affecting IRs of these severe congenital malformations.

The advice of the Dutch Health Council to offer a Tdap vaccination to all pregnant women in the Netherlands was published in 2015. A possible limitation of our study is that in 2018, i.e. before routine maternal vaccination began in December 2019, about 13% of pregnant women were already Tdap vaccinated at their own expense.[28] It was impossible to distinguish IRs for all outcomes between

women who were and were not immunised. However, data for 2018 were in line with data for 2016-2017 for all outcomes, and studies did not show any safety signals.[10-13] Therefore, we do not expect that vaccine coverage had much impact on the IRs discussed in this article.

Conclusions

Background incidences remain essential when monitoring the safety of an immunisation strategy, especially when a new age- or risk-group is targeted. We found several trends over time for adverse pregnancy outcomes that might be explained by changes in case definitions or standards of care. These data on the incidence of adverse events before the 2019 introduction of Tdap vaccination in the NIP allows more perspective on the incidence of such events since its implementation.

Supplementary materials

Supplementary Table 1. Case definitions as extracted from the DPR-database

Maternal outcomes	
maternal mortality	maternal death during pregnancy
placental abruption	as reported by midwife or obstetrician
hypertension	as reported by midwife or obstetrician according to the International Society for the Study of Hypertension in Pregnancy (ISSHP)
(pre-)eclampsia	(pre-)eclampsia with or without HELLP as reported by obstetrician
rupture of membranes ≥24h pre-labour	as reported by midwife or obstetrician
labour induction	as reported by obstetrician by amniotomy, foley catheter, prostaglandins, oxytocin or prostaglandins and oxytocin
vacuum delivery	as reported by obstetrician
forceps delivery	as reported by obstetrician
caesarian section	primary or secondary section as reported by obstetrician
uterine rupture	as reported by obstetrician
postpartum hemorrhage	blood loss of ≥1000 mL in the first 24h after delivery, as reported by midwife or obstetrician
Neonatal outcomes	
stillbirth	death before or during labour
neonatal mortality	death within the first 28 days after birth
perinatal mortality	stillbirth and neonatal combined, up to 7 days or 28 days after birth
prematurity <28 w and <37 w GA	birth before 196 or 259 days GA respectively, as reported by midwife or obstetrician
small and large for gestational age	according to Hoftiezer charts, in which percentiles of birth weight versus GA have been calculated for each case. SGA was defined as cases with <10^{th} percentile, LGA was defined as cases with >90^{th} percentile according to Hoftiezer et al.
severe congenital malformations	one of the following: meningo(myelo)cele, neuromuscular disorders, transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart

	syndrome, coarctatio aortae, tricuspid atresia/stenosis, complex cardiac anomaly, esophagus atresia/stenosis/fistula, intestinal atresia, Hirschsprung's disease, malrotation/volvulus, atresia choanae, congenital tracheal malformations, oligohydramnion, congenital lobar emphysema, congenital cystic adenomatoid malformation, hydro/chylothorax, diaphragmatic hernia, diaphragmatic relaxation, exstrophia vesicae, bilateral renal agenesis, gastroschisis, omphalocele, inborn errors of metabolism, congenital malignancy.
low Apgar score	as reported <7 at 5 min
resuscitation	as reported by care provider
neonatal hospital admission	as reported by pediatrician. For hospitalisations after caesarian section, a specific diagnosis was required
Neonatal Intensive Care Unit admission	as reported by neonatologist
Idiopathic respiratory distress syndrome (IRDS)	as reported by pediatrician
neonatal sepsis	as reported by pediatrician
neonatal infections, including sepsis	as reported by pediatrician

References

1. van der Maas NA, van Aerde K, Bont LJ, Bekker MN, Rots N, de Melker HE. [Infection prevention in newborns through maternal vaccination: current insights and developments]. *Ned Tijdschr Geneeskd* 2016; **160**: D411.
2. Vegelin AL, van Vught AJ, Wolfs TF, Kimpen JL, Geelen SP. [Pertussis in young infants]. *Ned Tijdschr Geneeskd* 1998; **142**(49): 2657-60.
3. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014; **384**(9953): 1521-8.
4. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. *Clin Infect Dis* 2017; **64**(1): 3-8.
5. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *Clin Infect Dis* 2016; **62**(7): 829-36.
6. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization. *Clin Infect Dis* 2017; **64**(8): 1129-32.
7. Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA* 2014; **311**(17): 1760-9.
8. Maertens K, Cabore RN, Huygen K, Hens N, Van Damme P, Leuridan E. Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. *Vaccine* 2016; **34**(1): 142-50.
9. Fortner KB, Swamy GK, Broder KR, et al. Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women. *Vaccine* 2018; **36**(42): 6354-60.
10. McMillan M, Clarke M, Parrella A, Fell DB, Amirthalingam G, Marshall HS. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. *Obstet Gynecol* 2017; **129**(3): 560-73.
11. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. *JAMA* 2014; **312**(18): 1897-904.
12. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ* 2014; **349**: g4219.
13. Gkentzi D, Katsakiori P, Marangos M, et al. Maternal vaccination against pertussis: a systematic review of the recent literature. *Arch Dis Child Fetal Neonatal Ed* 2017; **102**(5): F456-F63.
14. Layton JB, Butler AM, Li D, et al. Prenatal Tdap immunization and risk of maternal and newborn adverse events. *Vaccine* 2017; **35**(33): 4072-8.
15. DeSilva M, Vazquez-Benitez G, Nordin JD, et al. Maternal Tdap vaccination and risk of infant morbidity. *Vaccine* 2017; **35**(29): 3655-60.
16. Vygen-Bonnet S, Hellenbrand W, Garbe E, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. *BMC Infect Dis* 2020; **20**(1): 136.
17. The Netherlands Perinatal Registry. 2019. www.perined.nl.
18. CCMO - Legal gramework for medical scientific research. 2019. https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not.
19. Hoftiezer L, Hukkelhoven CW, Hogeveen M, Straatman HM, van Lingen RA. Defining small-for-gestational-age: prescriptive versus descriptive birthweight standards. *Eur J Pediatr* 2016; **175**(8): 1047-57.
20. Guidelines Serotinity. 2007. https://www.nvog.nl/wp-content/uploads/2017/12/Serotiniteit-2.0-08-06-2007.pdf.
21. Grobman WA, Rice MM, Reddy UM, et al. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. *N Engl J Med* 2018; **379**(6): 513-23.
22. Miller NR, Cypher RL, Foglia LM, Pates JA, Nielsen PE. Elective Induction of Labor Compared With Expectant Management of Nulliparous Women at 39 Weeks of Gestation: A Randomized Controlled Trial. *Obstet Gynecol* 2015; **126**(6): 1258-64.

23. Grevinga M.; Schönbeck YH-M, A.D.; Reijnders, M.E.B.; Detmar, S.B. . Aangeboren afwijkingen in Nederland 2010-2016: Gebaseerd op de Landelijke Perinatale Registraties, 2018.
24. Zegers MJ, Hukkelhoven CW, Uiterwaal CS, Kollee LA, Groenendaal F. Changing Dutch approach and trends in short-term outcome of periviable preterms. *Arch Dis Child Fetal Neonatal Ed* 2016; **101**(5): F391-6.
25. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol* 2010; **37**(2): 339-54.
26. Griffin JB, Yu L, Watson D, et al. Pertussis Immunisation in Pregnancy Safety (PIPS) Study: A retrospective cohort study of safety outcomes in pregnant women vaccinated with Tdap vaccine. *Vaccine* 2018; **36**(34): 5173-9.
27. Hall C, Abramovitz LM, Bukowinski AT, et al. Safety of tetanus, diphtheria, and acellular pertussis vaccination among pregnant active duty U.S. military women. *Vaccine* 2020; **38**(8): 1982-8.
28. Schurink-van 't Klooster TM, De Melker HE. The National Immunization Programme in the Netherlands 2018 - 2019, 2020.

CHAPTER 8

Circulation of *Bordetella pertussis* in the Caribbean Netherlands: a population-based seroepidemiological study

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Abstract

Objectives

Pertussis is a respiratory infectious disease caused by *Bordetella pertussis*. In the Caribbean Netherlands (CN), comprising the islands Bonaire, St. Eustatius, and Saba, registration of cases is mandatory for disease surveillance. However, insufficient laboratory facilities hamper case confirmation and circulation persists. The aim of this seroepidemiological study is to gain insight into *B. pertussis* circulation in CN and to investigate what factors contribute to the risk of infection.

Methods

Blood samples and questionnaires were collected for 1,829 participants 0-90 years old. Concentrations of *B. pertussis* toxin-specific IgG antibodies (anti-Pt) were determined using a bead-based immunoassay to indicate infections within the previous twelve months (based on anti-Pt ≥50IU/mL) in participants without detectable vaccine-induced humoral immunity. Risk factors for a recent infection were analyzed using logistic regression models.

Results

An estimated 8.2% (95% CI 6.6-10.1) of CN residents aged ≥9 years was recently infected by *B. pertussis*. Risk factors for a recent infection were age 12-29 years (13.8%-14.6%) and Dutch Caribbean or Surinamese origin (10.7%).

Conclusions

B. pertussis infections occur frequently among CN residents aged ≥9 years, although few clinical pertussis cases are reported. Transmission to vulnerable individuals seems likely and should be taken into account in optimizing the vaccination program.

Introduction

Pertussis or whooping cough is a highly contagious respiratory disease caused mainly by the bacterium *Bordetella pertussis*. Infants too young to be vaccinated are the most vulnerable to severe complications, e.g., pneumonia, which often leads to hospitalization and sometimes death.[1,2] These infants depend on placentally-transferred maternal antibodies for protection against disease.[3,4] In older children and adults, pertussis often manifests mildly and symptoms remain unrecognized, whereas adults with comorbidities and elderly are at higher risk of severe pertussis complications and hospitalization.[5-7] Hence, *B. pertussis* is known to circulate across all age groups in many countries despite high vaccination coverage; it is readily transmitted by infected persons showing no typical clinical symptoms.[8-10]

The Caribbean Netherlands (CN) is situated in the Caribbean Sea and comprises three Dutch special municipalities: Bonaire (one of the three Dutch Leeward Antilles along with Aruba and Curaçao), St. Eustatius, and Saba. The latter two, also described as the Windward Islands, are 30 km apart and about 800 km northeast of Bonaire, near St. Maarten. Hexavalent vaccines containing *B. pertussis*-specific antigens are administered to infants in CN at 2, 3 and 4 months (m) of age, with booster doses at 11m and 4 years (y) of age.[11] Booster vaccination at the age of 4y was implemented on Saba in 2008, Bonaire in 2014, and St. Eustatius in 2016. In 2017, vaccination coverage for infants younger than 2y ranged between 93-100% on the CN islands.[12] Pertussis cases must be reported and requires laboratory confirmation.[13] In 2017 on Bonaire, six confirmed cases of clinical pertussis were reported, including two unvaccinated neonates, two children aged 1 and 12y, and two adults.[14] These represented an incidence of 30 per 100,000 on Bonaire (total number of residents on Bonaire is ~20,000) vs 2.5 per 100,000 in Latin America on average from 2000-2015 and 28.7 per 100,000 in the Netherlands in 2017.[13,15] St. Eustatius and Saba reported some suspected pertussis cases, but they were not confirmed due to a lack of laboratory facilities.[13] Clinical diagnosis also depends on the awareness of general practitioners of pertussis disease, particularly its mild form, and the reluctance of the public to seek medical attention. Incidence rates based on case reporting are therefore likely to be underestimated.[16] These challenges to accurate pertussis disease surveillance emphasize the need for alternative surveillance strategies.

Antibodies are induced shortly after natural *B. pertussis* infection or immunization and wane to half their peak concentration in 12-20m.[17] In recently

vaccinated people, high concentrations of IgG against *B. pertussis* toxin (Pt) reflect a vaccine-induced antibody response. In persons not vaccinated within the last five years, a concentration of anti-Pt IgG ≥50 international units (IU) /mL indicates an infection within the last 12 months.[8,16] Lower concentrations of anti-Pt IgG point to less recent pertussis infections.[18] The two-fold aim of this seroepidemiological study is to gain knowledge about the circulation of *B. pertussis* on the islands of CN by tracing the frequency of recent infections and moreover to investigate the risk factors of getting infected with *B. pertussis*.

Methods

Population and setting

Details of the study design, data collection and sample size calculation have been described previously.[19] Briefly, on each island an age-stratified random sample of people aged 0–11, 12–17, 18–34, 35–59 and 60–90y was drawn from the population registry (PIVA-V, January 1, 2017). In total, 8,068 residents were invited for participation (Bonaire n = 4,798; St. Eustatius n = 2,135; and Saba n = 1,135), based on an age-specific precision ranging between 5.5% and 10% , an alpha of 5%, and an expected response rate of 30%. For each participant, a blood sample was taken by finger prick (or heel prick for infants) and collected as dried blood spots on Whatman® 903 protein-saver cards. Subsequently, a questionnaire and vaccination certificate for each participant were shared with the research staff. If certificates were unavailable, records were requested from the local public health service or hospital. Informed consent was provided by each participant or his/her guardian.

Laboratory analyses

Blood samples were transferred to the National Institute for Public Health and the Environment (RIVM) in the Netherlands and stored at -80°C, awaiting analyses. A 3.2mm punch was taken from dried blood spots and incubated in assay buffer (PBS supplemented with 3% BSA and 0.1% Tween-20) at 4°C overnight on a shaker to release serum.[20,21] Sera were tested at 1:200 and 1:4,000 dilutions. Concentrations of anti-Pt IgG were determined by a fluorescent bead-based immunoassay using a Luminex LX200 machine.[22] Standard sera and controls were used on each plate, and sera were calibrated against the World Health Organization International Standard Pertussis Anti-serum (serum reference 06/140). Native Pt (Netherlands Vaccine Institute, no peg004) was used. The lower limit of quantification was restricted by the number of dilutions made for the

reference line and therefore, 0.85 IU/mL was used in our dataset.

Statistical analyses – age-specific prevalence of increased anti-Pt IgG and geometric mean concentrations (GMC)

Analyses were performed using R software, version 4.0.4. Anti-Pt IgG concentrations were divided into four categories: ≥100 IU/mL; 50-<100 IU/mL; 5-<50 IU/mL; and <5 IU/mL. For persons aged 9y and older and unvaccinated children, these categories indicate recent infection in the previous 6m (≥100 IU/mL) or in the previous 6-12m (50-<100 IU/mL) or no recent infection (5-<50 IU/mL and <5 IU/mL). The cut-offs were based on studies investigating anti-Pt IgG concentrations in relation to waning immunity following vaccination and (re)infection.[10,18,23] Recent infections in the previous 12 months were used as the primary outcome, and recent infections during the previous 6 months as secondary outcome. Anti-Pt IgG concentrations induced by the booster vaccination at ~4y of age may increase up to 9y of age (fig 1A) and thus interfere with analyses to determine recent infections. To ensure that increased concentrations are due to a recent infection and not falsely induced by a missed vaccination, children younger than 9y were excluded from the analyses. This cut-off was set at 9y because the booster vaccine at ~4y is administered at a school-based program, and the time of its administration may fluctuate.

Participants were assigned sampling weights to match the population distribution on each island, taking into account age, sex, and country of birth (and neighborhood for residents of Bonaire). Weighted age-specific prevalence with corresponding 95% confidence intervals (CI) were estimated. To increase power, participants from St. Eustatius and Saba were combined into a Windward Islands category, which is justified by their close proximity and comparable overall characteristics. Absolute anti-Pt IgG concentrations were log-transformed and expressed in GMCs with corresponding 95% CIs.

Statistical analyses – risk factors for a recent infection

Univariable logistic regression was used to identify potential risk factors for a recent infection in the previous 12 months (anti-Pt IgG ≥50 IU/mL) among participants aged 9y and older. Participants with missing values for ethnic background (n=13), household size (n=7), and those who were vaccinated in the previous five years (n=4) were excluded from the analyses (total remaining n=1484). The following variables were investigated: island of residence, sex, age group, maternal education level, household size, number of "yesterday's contacts" (i.e., on day before completing questionnaire), and ethnic background as defined

by origin in Dutch Caribbean territories (Bonaire, Saba and St. Eustatius) and Aruba, Curaçao, and St. Maarten, plus Suriname, a former Dutch colony on the northeastern coast of South America. The median number of yesterday's contacts was calculated for each age group separately, and participants were subsequently categorized as equal/higher or lower than the median.

Variables with a p-value of <0.10 in the univariable analyses were selected for multivariable logistic regression, along with a priori controlling for age group and island of residence following the sample design. Individual variables contributing to the risk of infection were identified by performing stepwise backward selection. A p-value of <0.05 was considered significant. Odds ratios (OR), corresponding 95% CIs, and p-values of variables in univariable analyses and multivariable analyses were provided. Sensitivity analyses were performed exploring recent infections in the previous 6 months (anti-Pt IgG ≥100 IU/mL) as the dependent variable (appendix 2).

Results

Study sample and demographics

This study included 1,900 participants, of whom 1,829 persons or their guardians provided a questionnaire and blood sample. Most of them resided on Bonaire: 1,129 (61.7%), followed by St. Eustatius: 477 (26.1%), and Saba: 223 (12.2%) (table 1). Participants' age ranged from 3m to 90y, and 824 (45.1%) were male. Most participants originated from the Dutch Caribbean territories or Suriname (1,312, 72.2%), followed by Latin America or other non-Western countries (281, 15.5%), and European Netherlands or other Western countries (223, 12.2%). The majority of children under 9y (265 of 321; 82.5%) had been vaccinated against pertussis at least four times; 38 (11.8%) had received up to three doses, and 18 (5.6%) were most likely unvaccinated. Six participants were vaccinated against pertussis at 9y or older, and four of these were vaccinated in the past five years.

Age-specific GMC and prevalence of increased anti-Pt IgG concentration

Among children who received at least one vaccination, anti-Pt IgG had waned to the lowest concentrations by age 9y (figure 1A). Overall weighted prevalence of a recent infection in the previous 12 months and GMCs among age groups <9y generally followed the vaccination schedule (appendix 1). Peak GMCs were found within the ages directly after the primary vaccination series, i.e., 0 and 1y. After antibodies had waned, GMCs significantly increased again in the ages after booster vaccination, i.e., ~4y of age; 12.9 IU/mL at 3y vs 39.0 IU/mL at 4-6y. The GMC

decreased significantly at the age of 7-8y (8.3 IU/mL, 95% CI 5.8-11.8), well below the cut-off for recent infection at 50 IU/mL.

The overall weighted prevalence of recent infections in the previous 12 months in the ≥9y CN-population was 8.2% (95% CI 6.6-10.1). This was highest on Bonaire (8.6%, 95% CI 6.6-10.9), followed by St. Eustatius (7.4%, 95% CI 4.7-11.0) and Saba (5.7%, 95% CI 2.9-10.0). Participants aged 12-17y and 18-29y had the highest prevalence of recent infections in the previous 12 months, i.e., 16.1% (95% CI 11.5-22.6) and 16.7% (95% CI 10.4-24.9), respectively (figure 1B). The lowest prevalence was in age group 30-44y, with 4.8% (95% CI 2.4-8.6). Corresponding GMCs of anti-Pt IgG for the age groups of 12-17y and 18-29y were 8.9 IU/mL (95% CI 7.2-10.9) and 8.5 IU/mL (95% CI 6.2-11.5), respectively, and the GMC for 12-17y-olds was significantly higher than for 30-44y-olds (5.8 IU/mL, 95% CI 4.8-7.0) (figure 1B). Subsequently, GMCs of anti-Pt IgG gradually increased in age groups ≥45y, but not significantly. Among 9-17y-olds, the frequency of recent infections in the previous 12 months differed across the islands of CN, with 14.9%, 95% CI 10.6-20.2 on Bonaire vs 5.5%, 95% CI 2.7-10.0 on the Windward Islands (figure 2A). Among 60-90y-olds, the frequency was higher on the Windward Islands (13.1, 95% CI 7.5-20.6) than Bonaire (6.4, 95% CI 3.8-9.9), but not significantly.

Risk factors for a recent infection

Among 1,484 participants of age ≥9y in CN, 134 were infected in the previous 12 months. In both univariable and multivariable analyses, age group and ethnic background were significant risk factors for a recent infection (table 2). The odds were higher in participants of 9-17y and 18-29y compared to participants of 30-44y (adjusted ORs 2.5, 95% CI 1.3-5.2, and 2.8, 95% CI 1.4-6.0, respectively). Participants originating from the European Netherlands or other Western countries had lower odds for recent infection compared to participants originating from the Dutch Caribbean territories or Suriname (adjusted OR 0.4, 95% CI 0.2-0.8). In sensitivity analyses exploring the outcome of recent infections in the previous six months (anti-Pt IgG ≥100 IU/mL, n=53), significantly associated risk factors included island of residence (adjusted OR for Bonaire vs Windward Islands 3.6, 95% CI 1.8-8.2) and ethnic background (adjusted OR for Latin America or other non-Western countries vs Dutch Caribbean territories or Suriname 0.3, 95% CI 0.1-0.9) (appendix 2). ORs for different age groups were in line with the main analysis, but not significantly.

Table 1. Sociodemographic characteristics and vaccination history of participants with a blood sample in the Health Study Caribbean Netherlands by island.

Sociodemographic Characteristics and Vaccination History	Bonaire n (%) n = 1129 (61.7)	St. Eustatius n (%) n = 477 (26.1)	Saba n (%) n = 223 (12.2)	Total n (%) n = 1829
Sex				
Male	506 (44.8)	221 (46.3)	97 (43.5)	824 (45.1)
Female	623 (55.2)	256 (53.7)	126 (56.5)	1005 (54.9)
Age group, years				
0-8	197 (17.4)	87 (18.2)	37 (16.6)	321 (17.6)
9-17	255 (22.6)	127 (26.6)	37 (16.6)	419 (22.9)
18-29	103 (9.1)	49 (10.3)	23 (10.3)	175 (9.6)
30-44	136 (12.0)	68 (14.3)	34 (15.2)	238 (13.0)
45-59	163 (14.4)	65 (13.6)	35 (15.7)	263 (14.4)
60-90	275 (24.4)	81 (17.0)	57 (25.6)	413 (22.6)
Ethnic background*				
Dutch Caribbean territories[a] or Suriname	803 (71.2)	383 (82.0)	126 (57.0)	1312 (72.2)
European Netherlands or other Western countries	143 (12.7)	30 (6.4)	50 (22.6)	223 (12.3)
Latin America or other non-Western countries	182 (16.1)	54 (11.6)	45 (20.4)	281 (15.5)
(Maternal) education level[b]				
High	172 (15.2)	68 (14.3)	87 (39.0)	327 (17.9)
Middle	298 (26.4)	125 (26.2)	45 (20.2)	468 (25.6)
Low	571 (50.6)	232 (48.6)	80 (35.9)	883 (48.3)
Unknown	88 (7.8)	52 (10.9)	11 (4.9)	151 (8.2)
Monthly gross income				
High (≥$3001)	197 (17.4)	91 (19.1)	60 (26.9)	348 (19.0)
Middle ($1501–3000)	328 (29.1)	88 (18.5)	60 (26.9)	476 (26.0)
Low (<$1500)	329 (29.1)	133 (27.8)	56 (25.1	518 (28.3)
Does not want to answer	106 (9.4)	73 (15.3)	23 (10.3)	202 (11.1)

Table 1. Continued.

Sociodemographic Characteristics and Vaccination History	Bonaire n (%) n = 1129 (61.7)	St. Eustatius n (%) n = 477 (26.1)	Saba n (%) n = 223 (12.2)	Total n (%) n = 1829
Unknown	169 (15.0)	92 (19.3)	24 (10.8)	285 (15.6)
Number of contacts yesterday				
Higher or equal to the median per age group[c]	532 (47.1)	163 (34.2)	62 (27.8)	757 (41.4)
Lower than median per age group	520 (46.1)	204 (42.8)	132 (59.2)	856 (46.8)
Unknown	77 (6.8)	110 (23.1)	29 (13.0)	216 (11.8)
Household size, persons				
Single-person household	139 (12.3)	51 (10.7)	31 (13.9)	221 (12.1)
2-5	864 (76.5)	350 (73.4)	176 (78.9)	1390 (76.0)
≥6	119 (10.5)	72 (15.1)	13 (5.8)	204 (11.2)
Unknown	7 (0.6)	4 (0.8)	3 (1.3)	14 (0.8)
Vaccination history against pertussis[d]				
4 or more doses	422 (37.4)	226 (47.4)	75 (33.6)	723 (39.5)
1-3 doses	68 (6.0)	35 (7.3)	10 (4.5)	113 (6.2)
(partly) participated in national immunization program (self-reported)	498 (44.1)	151 (31.7)	107 (48.0)	756 (41.3)
Unvaccinated	141 (12.5)	65 (13.6)	31 (13.9)	237 (13.0)

a. Dutch Caribbean territories include Bonaire, St. Eustatius and Saba (CN) plus Aruba, Curaçao and St. Maarten. For participants with an ethnic background in European Netherlands or other Western countries, 147 (66%) were Dutch. Within the ethnic background of Latin America and other non-Western countries, 261 (93%) were born in Latin America. b. Maternal educational level was used for participants 0–11y, active education was used for participants 12–25y and highest accomplished educational level was used for participants >25 y. Low = no education, primary school, pre-vocational education (VMBO), lower vocational education (LBO/MBO-1) and lower general secondary education (MAVO/VMBO). Middle = intermediate/secondary vocational education (MBO-2-4), higher/senior vocational education (HAVO) and pre-university education (VWO/Gymnasium); high = higher

professional education (HBO), university BSc., university MSc. and doctorate. c. Overall median number of contacts yesterday was 8. d. 94.4% of children under 9y received at least one vaccination against pertussis. * Missing data: 13 ethnic background

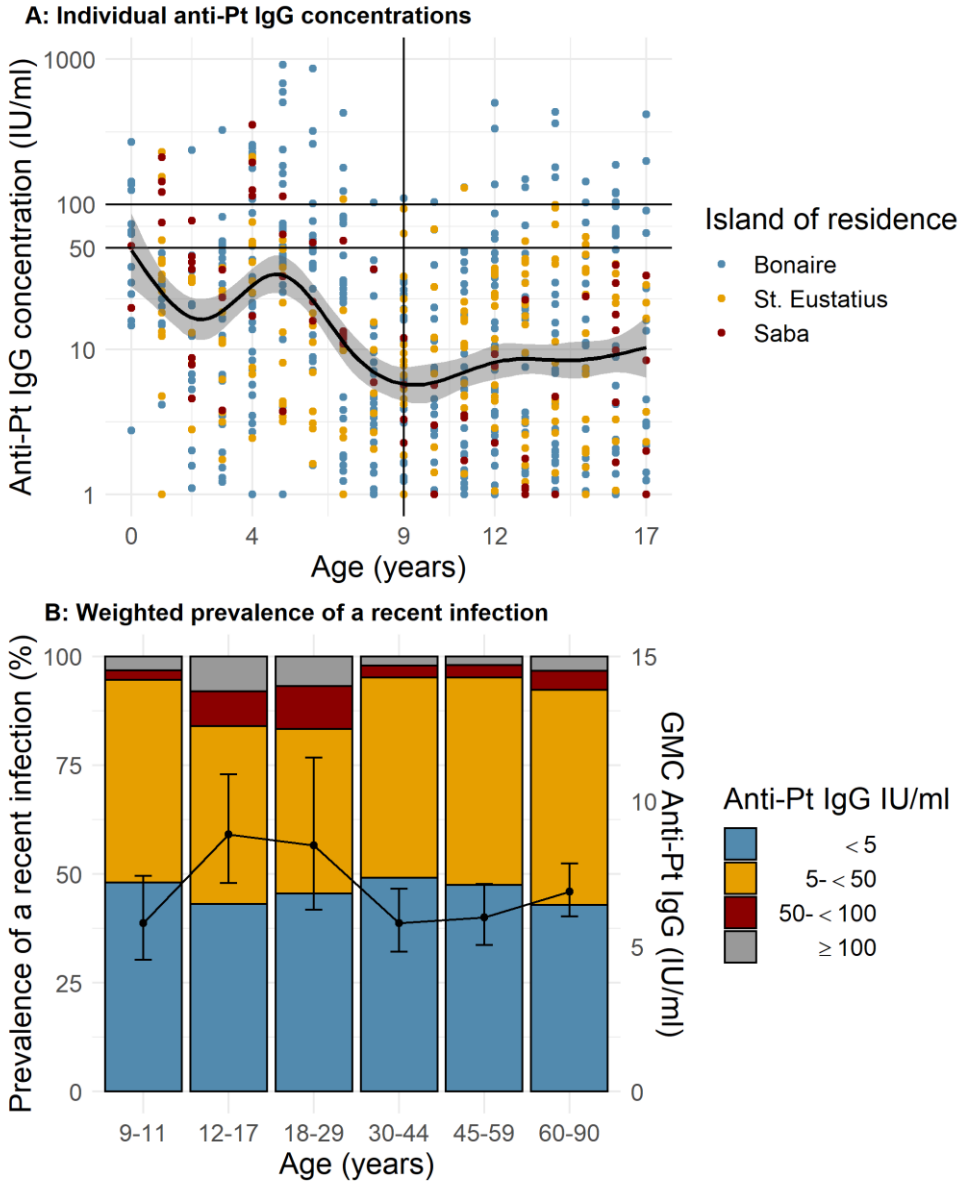


Figure 1. Individual anti-Pt IgG concentrations (IU/mL) and weighted age-specific prevalence of a recent infection and GMCs. Panel A reflects vaccine-induced responses of anti-Pt in children who received at least one pertussis-containing vaccine. The generalized additive model spline with 8 knots indicates waning of anti-Pt IgG; a cut-off for the arbitrary age when children may be yet susceptible for *B.*

pertussis infection was placed at 9y (lowest concentration anti-Pt IgG in this graph). Panel B shows the prevalence of recent infection in four categories: twice no recent infection (<5 IU/mL or 5-<50 IU/mL), between the last six and twelve months (50-<100 IU/mL) and in the previous six months (≥100 IU/mL). It also shows GMCs with corresponding 95% CIs.

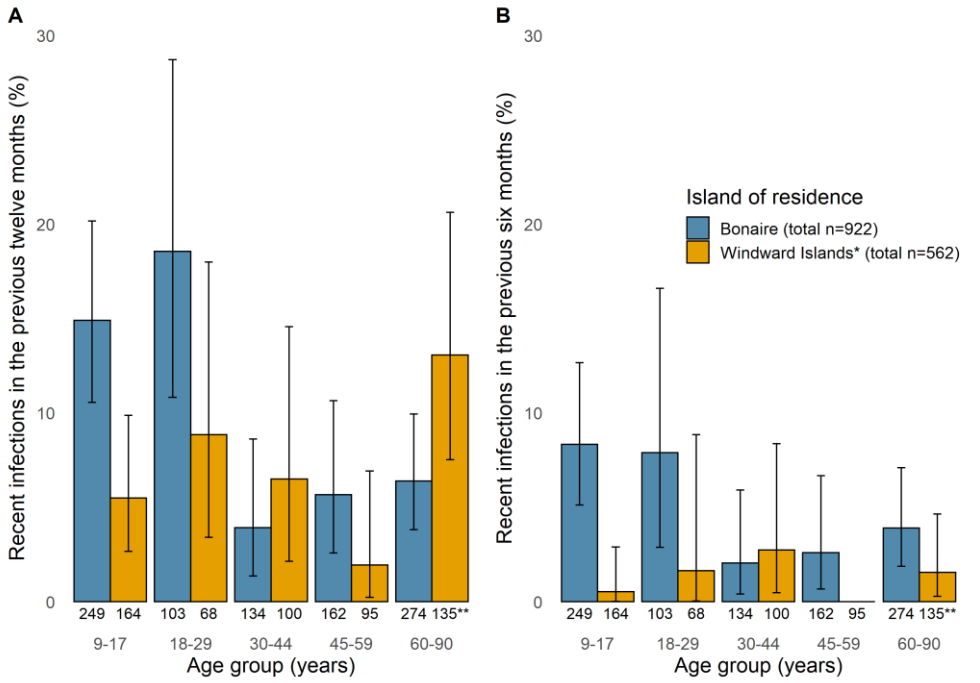


Figure 2. Weighted age-specific prevalence of a recent infection in the previous twelve months (anti-Pt IgG concentration ≥50; panel A) or in the previous six months (anti-Pt IgG concentration ≥100 IU/mL; panel B), stratified for island of residence, with 95% CIs. * The Windward Islands include St. Eustatius and Saba. ** Number of participants per age group and island of residence

Discussion

This is the first seroepidemiological study to investigate recent *B. pertussis* infections in the general population of CN, comprising the islands of Bonaire, St. Eustatius and Saba. Overall, an estimated 8.2% of CN residents aged ≥9y were recently infected in the previous 12 months. The highest rates were seen in adolescents of 12-17y and young adults of 18-29y. These results emphasize that *B. pertussis* is circulating in the general CN population and that circulation is vastly underestimated using reporting systems for clinical pertussis cases. Furthermore, participants who reside on Bonaire and participants originating from the Dutch Caribbean territories or Suriname were most likely to be recently infected with *B. pertussis*.

Table 2. Risk factor analysis for a recent infection in the previous twelve months (anti-Pt ≥50 IU/mL) among participants of 9 years and older in the Caribbean Netherlands population.

Potential Risk Factor for infection	n (%) n = 1484*	n (%) anti-Pt ≥50 IU/mL n = 134 (9.0)	Univariable Crude OR (95% CI)	p-value	Multivariable Adjusted OR (95% CI)	p-value
Island				0.364		0.522
Bonaire	922 (62.1)	89 (9.7)	1.2 (0.8-1.9)		1.3 (0.8-2.0)	
St. Eustatius	378 (25.5)	31 (8.2)	Ref.		Ref.	
Saba	184 (12.4)	14 (7.6)	0.9 (0.5-1.8)		1.1 (0.6-2.2)	
Sex				0.955		
Male	645 (43.5)	58 (9.0)	Ref.			
Female	839 (56.5)	76 (9.1)	1.0 (0.7-1.5)			
Age group, years				**<0.0001**		**<0.001**
9-11	124 (8.4)	8 (6.9)	1.3 (0.5-3.2)		1.1 (0.4-2.7)	
12-17	289 (19.5)	40 (13.8)	3.0 (1.6-6.1)		2.5 (1.3-5.2)	
18-29	171 (11.5)	25 (14.6)	3.2 (1.6-6.7)		2.8 (1.4-6.0)	
30-44	234 (15.8)	12 (5.1)	Ref.		Ref.	
45-59	257 (17.3)	11 (4.3)	0.8 (0.4-1.9)		0.8 (0.4-1.9)	
60-90	409 (27.6)	38 (9.3)	1.9 (1.0-3.9)		1.8 (0.9-3.6)	
Ethnic background*				**<0.0001**		**0.016**
Dutch Caribbean territories or Suriname	1016 (68.5)	109 (10.7)	Ref.		Ref.	
European Netherlands or other Western countries	199 (13.4)	8 (4.0)	0.4 (0.2-0.7)		0.4 (0.2-0.8)	

Table 2. Continued.

Potential Risk Factor for infection	n (%) n = 1484*	n (%) anti-Pt ≥50 IU/mL n = 134 (9.0)	Univariable Crude OR (95% CI)	p-value	Multivariable Adjusted OR (95% CI)	p-value
Latin America or other non-Western countries	269 (18.1)	17 (6.3)	0.6 (0.3-0.9)		0.6 (0.4-1.0)	
(Maternal) education level				0.318		
High	257 (17.3)	22 (8.6)	Ref.			
Middle	353 (23.8)	32 (9.1)	1.1 (0.6-1.9)			
Low	754 (50.8)	73 (9.7)	1.2 (0.7-1.9)			
Unknown	120 (8.1)	7 (5.8)	0.7 (0.3-1.5)			
Number of contacts yesterday				0.677		
Higher or equal to the median per age group[a]	626 (42.2)	61 (9.7)	1.0 (0.5-1.5)			
Lower than median per age group	686 (46.2)	55 (9.3)	Ref.			
Unknown	172 (11.6)	18 (10.5)	1.2 (0.7-2.1)			
Household size, persons*				0.450		
Single-person household	218 (14.7)	16 (7.3)	Ref.			
2-5	1112 (74.9)	103 (9.3)	1.3 (0.8-2.3)			
≥6	154 (10.4)	15 (9.7)	1.4 (0.7-2.9)			

a. Overall median number of contacts yesterday was 8. * Missing data: 13 ethnic background, 7 household size, 4 vaccinated against pertussis in the past five years.

The highest frequency of recent infections with *B. pertussis* in the previous twelve months was seen in 12-17y and 18-29y-olds, with estimates at 16.1% and 16.7%, respectively. Such high percentages suggest that despite vaccination, adolescents and young adults are susceptible to contracting pertussis. Their vaccine-induced immunity may have waned, as the fifth dose of a pertussis vaccine (the 4-year booster dose for CN) provides protection for approximately five years.[24,25] Once infected, adolescents may readily transmit *B. pertussis* due to clustering in secondary schools.[26,27] The source of infection for adolescents probably lies in fellow schoolmates, from whom it can be passed on to vulnerable individuals such as unvaccinated infants. Additionally, GMCs of anti-Pt IgG seemed to increase gradually between 45y- and 90y-olds. The source for exposure in these age groups may lie in the 12-29y-olds, since 35% of 45-59y-old participants in this study reported living in a household with at least one person between 12-29y of age. Moreover, repeated exposure to B. pertussis at older ages may cause longer duration of memory against Pt, which may also explain rises in GMCs in ≥45y-olds.[28] The high frequency of recent B. pertussis infections among participants originating from the Dutch Caribbean territories or Suriname is not well understood. We hypothesize that such differences for ethnic backgrounds could be related to travel behavior or tourism and work on the islands of CN, which contributes to *B. pertussis* circulation. Additionally, residents of CN may have families in the Netherlands or other European countries, where *B. pertussis* is also known to circulate in the population. Further data on this topic are lacking and remain implicated for future research.

A global interpretation of recent *B. pertussis* infections based on serology has been provided in a review that assessed many population-based studies in countries with different vaccination programs.[16] The authors concluded that the number of pertussis cases is underestimated in many countries, which is similar to our results. They also confirmed that the frequency of a recent infection with *B. pertussis* depends on age, with peak anti-Pt IgG concentrations in adolescents and young adults in studies from Finland, France, the Netherlands, East Germany, Denmark, the USA and Gambia.[29-36] To our knowledge, only one population-based serosurveillance study has been performed in Latin America. This study was also included in the above mentioned review. In the Mexican population in 2010, the highest proportion of recent infections (based on anti-Pt IgG ≥44 IU/mL) was seen in 50-59y-olds.[37] In contrast to our study, the authors reported no increased risk for a recent infection in adolescents and young adults. This dissimilarity may reflect the fact that Mexican and CN children were vaccinated according to a

different vaccination schedule. Also, the Mexican study was conducted before a large pertussis epidemic in 2012, which could have led to lower anti-Pt IgG concentrations in younger age groups. In the European Netherlands, a nationwide serosurveillance study was conducted similarly and simultaneously to the present study (manuscript submitted for publication). Consistent with our results, the authors found an increased risk of a recent infection among adolescents and people living in larger households. Although the frequency of recent infections in large households was slightly higher in the current study, its association with CN could not be confirmed. Future seroepidemiological research in other Latin American countries may provide more insight into risk factors for a *B. pertussis* infection.

On Bonaire, the frequency of *B. pertussis* infections in the previous six months was significantly higher than on the Windward Islands, but frequency did not differ among the islands in the previous twelve months. This finding indicates that Bonaire participants might have been infected shortly before the current study began; it also emphasizes the lack of insight into *B. pertussis* circulation. Given the frequency of recent infections, we would expect higher numbers of clinical cases to be reported.[14] Enhanced disease surveillance could provide better insight into numbers of pertussis cases, particularly for individuals who are vulnerable for severe disease. As young infants are at risk of severe complications (and unvaccinated neonates were among Bonaire's reported infections), many countries now focus on maternal immunization to prevent transmission of *B. pertussis* to young infants. Maternal vaccination protects newborns in the first months of life by conferring passive immunity through transplacental antibody transfer. The Netherlands and the Latin American countries Argentina, Brazil, Chile, Colombia, Mexico, Panama and Saba have already introduced this strategy in their national immunization programs.[38] As CN generally follows the developments in the Dutch immunization program, Bonaire and St. Eustatius are expected to follow the Netherlands and Saba in adopting this strategy in the near future.

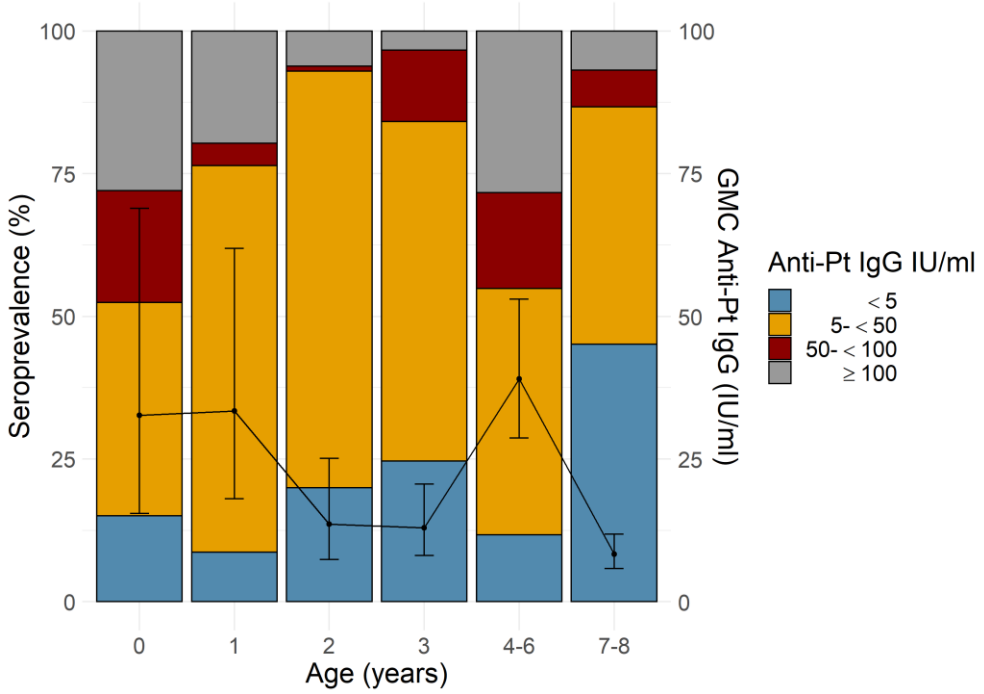
This study comes with limitations. In our study population, males were 45.1% vs 51.5% in the CN general population, and people originating from the Dutch Caribbean territories or Suriname were 72.2% of the study population vs. 59.4% in the general population.[39] We expect that these dissimilarities had little impact on the generalizability of our findings, as we used participants' sampling weights to correct for selective participation. Secondly, the absolute number of participants with a recent infection was low. Although a relatively large proportion of the population was sampled (7.5%), the low number of recent infections made it

challenging to detect small differences, and additional risk factors could have been missed. Lastly, although cut-offs of anti-Pt IgG are often used in seroepidemiological studies, some cases may still have sufficient anti-Pt IgG concentrations to be classified as recently infected, as waning sometimes manifests slower. Therefore, the actual number of recent infections may be overestimated and the recentness of infection must be interpreted with caution.[18]

Conclusion

This seroepidemiological study confirms that the circulation of *B. pertussis* in the general population of CN is vastly underestimated using its pertussis reporting systems. The transmission to vulnerable individuals seems likely and should be taken into account in optimizing the vaccination program. Seroepidemiological data should regularly be updated for understanding the circulation of *B. pertussis*.[40] Likewise, monitoring of pertussis epidemiology can be improved in CN by making mild cases more recognizable to the public and the medical community.

Supplementary materials



Appendix 1. Weighted age-specific prevalence (in categories displaying recent infection) and GMC with 95% CIs among children 0-8 years of age.

Appendix 2. Risk factor analysis for a recent infection in the previous six months (anti-Pt ≥100 IU/mL) among participants of 9 years and older in the Caribbean Netherlands population.

Potential Risk Factor for infection	n (%) n = 1484*	n (%) anti-Pt ≥100 IU/mL n = 53 (3.6)	Univariable Crude OR (95% CI)	p-value	Multivariable Adjusted OR (95% CI)	p-value
Island				**<0.0001**		**<0.001**
Bonaire	922 (62.1)	45 (4.9)	3.6 (1.8-8.2)		3.7 (1.8-8.6)	
Windward Islands	562 (37.9)	8 (1.4)	Ref.		Ref.	
Sex				0.320		
Male	645 (43.5)	25 (3.9)	Ref.			
Female	839 (56.5)	28 (3.3)	0.9 (0.5-1.5)			
Age group, years				**<0.0001**		0.167
9-11	124 (8.4)	4 (3.2)	1.3 (0.3-4.5)		1.0 (0.3-3.7)	
12-17	289 (19.5)	18 (6.2)	2.5 (1.0-7.1)		2.0 (0.8-5.7)	
18-29	171 (11.5)	8 (4.7)	1.9 (0.6-5.8)		1.6 (0.5-4.9)	
30-44	234 (15.8)	6 (2.6)	Ref.		Ref.	
45-59	257 (17.3)	4 (1.6)	0.6 (0.2-2.1)		0.6 (0.1-2.0)	
60-90	409 (27.6)	13 (3.2)	1.3 (0.5-3.6)		1.0 (0.4-2.9)	
Ethnic background*				**<0.0001**		**0.048**
Dutch Caribbean territories or Suriname	1016 (68.5)	45 (4.4)	Ref.		Ref.	
European Netherlands or other Western countries	199 (13.4)	4 (2.0)	0.4 (0.1-1.1)		0.5 (0.2-1.4)	

Appendix 2. Continued

Potential Risk Factor for infection	n (%) n = 1484*	n (%) anti-Pt ≥100 IU/mL n = 53 (3.6)	Univariable Crude OR (95% CI)	p-value	Multivariable Adjusted OR (95% CI)	p-value
Latin America or other non-Western countries	269 (18.1)	4 (1.5)	0.3 (1.1-0.8)		0.3 (0.1-0.9)	
(Maternal) education level				0.360		
High	257 (17.3)	8 (3.1)	Ref.			
Middle	353 (23.8)	12 (3.4)	1.1 (0.5-2.8)			
Low	754 (50.8)	30 (4.0)	1.3 (0.6-3.1)			
Unknown	120 (8.1)	3 (2.5)	0.8 (0.2-2.8)			
Number of contacts yesterday				**0.041**		0.167
Higher or equal to the median per age group[a]	626 (42.2)	24 (3.8)	1.0 (0.6-1.8)			
Lower than median per age group	686 (46.2)	26 (3.8)	Ref.			
Unknown	172 (11.6)	3 (1.7)	0.6 (0.2-1.3)			

Appendix 2. Continued

Potential Risk Factor for infection	n (%) n = 1484*	n (%) anti-Pt ≥100 IU/mL n = 53 (3.6)	Univariable Crude OR (95% CI)	p-value	Multivariable Adjusted OR (95% CI)	p-value
Household size, persons*				0.251		
Single-person household	218 (14.7)	6 (2.8)	Ref.			
2-5	1112 (74.9)	40 (3.6)	1.3 (0.6-3.5)			
≥6	154 (10.4)	7 (4.5)	1.7 (0.6-5.3)			
≥2 weeks persistent coughing in the last 3 months (self-reported)[b]				**0.002**		
Yes	151 (10.2)	9 (6.0)	1.8 (0.8-3.5)			
No	1174 (79.1)	41 (3.5)	Ref.			
Unknown	159 (10.7)	3 (1.7)	0.5 (0.1-1.5)			

a. Overall median number of contacts yesterday was 8. b. Persistent coughing was only reported for the risk factor analysis using the outcome of a recent infection in the previous six months. * Missing data: 13 ethnic background, 7 household size, 4 vaccinated against pertussis in the past five years.

References

1. van der Maas NA, van Aerde K, Bont LJ, Bekker MN, Rots N, de Melker HE. [Infection prevention in newborns through maternal vaccination: current insights and developments]. *Ned Tijdschr Geneeskd* 2016; **160**: D411.
2. Vegelin AL, van Vught AJ, Wolfs TF, Kimpen JL, Geelen SP. [Pertussis in young infants]. *Ned Tijdschr Geneeskd* 1998; **142**(49): 2657-60.
3. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014; **384**(9953): 1521-8.
4. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. *Clin Infect Dis* 2017; **64**(1): 3-8.
5. Kandeil W, Atanasov P, Avramioti D, Fu J, Demarteau N, Li X. The burden of pertussis in older adults: what is the role of vaccination? A systematic literature review. *Expert Rev Vaccines* 2019; **18**(5): 439-55.
6. Edwards K, Freeman DM. Adolescent and adult pertussis: disease burden and prevention. *Curr Opin Pediatr* 2006; **18**(1): 77-80.
7. Rothstein E, Edwards K. Health burden of pertussis in adolescents and adults. *Pediatr Infect Dis J* 2005; **24**(5 Suppl): S44-7.
8. Althouse BM, Scarpino SV. Asymptomatic transmission and the resurgence of Bordetella pertussis. *BMC Med* 2015; **13**: 146.
9. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. *Emerg Infect Dis* 2000; **6**(4): 348-57.
10. de Greeff SC, de Melker HE, van Gageldonk PG, et al. Seroprevalence of pertussis in The Netherlands: evidence for increased circulation of Bordetella pertussis. *PLoS One* 2010; **5**(12): e14183.
11. RIVM. Vaccination Schedule Bonaire, Saba and St. Eustatius [in Dutch: Vaccinatieschema Bonaire, Saba en St. Eustatius]. 2018.
https://rijksvaccinatieprogramma.nl/vaccinaties/vaccinatieschema (accessed October 29th 2020.
12. Van Lier EAG, J.L.E.; Oomen, P.J.; Giesbers, H.; van Vliet, J.A.; Drijfhout, I.H.; Zonnenberg-Hoff, I.F.; de Melker, H.E. Vaccination Coverage and Annual Report National Immunisation Programme Netherlands 2017 [in Dutch: Vaccinatiegraad en Jaarverslag Rijksvaccinatieprogramma Nederland 2017]: National Institute for Public Health and the Environment, Bilthoven, the Netherlands, 2018.
13. Schurink-van 't Klooster TM, de Melker HE. The National Immunisation Programme in the Netherlands - Surveillance en Developments in 2019-2020, 2020.
14. Schurink-van 't Klooster TM, de Melker HE. The National Immunization Programme in the Netherlands 2018 - 2019, 2020.
15. Folaranmi T, Pinell-McNamara V, Griffith M, Hao Y, Coronado F, Briere EC. Systematic review and meta-analysis of pertussis epidemiology in Latin America and the Caribbean: 1980-2015. *Rev Panam Salud Publica* 2017; **41**: e102.
16. Barkoff AM, Grondahl-Yli-Hannuksela K, He Q. Seroprevalence studies of pertussis: what have we learned from different immunized populations. *Pathog Dis* 2015; **73**(7).
17. Berbers GA, van de Wetering MS, van Gageldonk PG, Schellekens JF, Versteegh FG, Teunis PF. A novel method for evaluating natural and vaccine induced serological responses to Bordetella pertussis antigens. *Vaccine* 2013; **31**(36): 3732-8.
18. van der Lee S, Stoof SP, van Ravenhorst MB, et al. Enhanced Bordetella pertussis acquisition rate in adolescents during the 2012 epidemic in the Netherlands and evidence for prolonged antibody persistence after infection. *Euro Surveill* 2017; **22**(47).
19. Verberk JDM, Vos RA, Mollema L, et al. Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands. *BMC Infect Dis* 2019; **19**(1): 470.
20. Mei JV, Alexander JR, Adam BW, Hannon WH. Use of filter paper for the collection and analysis of human whole blood specimens. *J Nutr* 2001; **131**(5): 1631S-6S.
21. Hannon WH. Blood Collection on Filter Paper for Newborn Screening Programs. In Approved Standard, 6th ed.: Clinical and Laboratory Standards Institute: Wayne, PA, USA; 2013.

22. van Gageldonk PG, van Schaijk FG, van der Klis FR, Berbers GA. Development and validation of a multiplex immunoassay for the simultaneous determination of serum antibodies to Bordetella pertussis, diphtheria and tetanus. *J Immunol Methods* 2008; **335**(1-2): 79-89.
23. de Melker HE, Versteegh FG, Conyn-Van Spaendonck MA, et al. Specificity and sensitivity of high levels of immunoglobulin G antibodies against pertussis toxin in a single serum sample for diagnosis of infection with Bordetella pertussis. *J Clin Microbiol* 2000; **38**(2): 800-6.
24. McGirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. *Pediatrics* 2015; **135**(2): 331-43.
25. van der Lee S, Sanders EAM, Berbers GAM, Buisman AM. Whole-cell or acellular pertussis vaccination in infancy determines IgG subclass profiles to DTaP booster vaccination. *Vaccine* 2018; **36**(2): 220-6.
26. Wu Y, Zhu B, Gao Y, et al. Clustered cases of Bordetella pertussis infection cause high levels of IgG antibodies against pertussis toxin in adolescents in Gaobeidian city, China. *Epidemiol Infect* 2014; **142**(4): 738-43.
27. De Serres G, Shadmani R, Duval B, et al. Morbidity of pertussis in adolescents and adults. *J Infect Dis* 2000; **182**(1): 174-9.
28. Barkoff AM, Grondahl-Yli-Hannuksela K, Vuononvirta J, Mertsola J, Kallonen T, He Q. Differences in avidity of IgG antibodies to pertussis toxin after acellular pertussis booster vaccination and natural infection. *Vaccine* 2012; **30**(48): 6897-902.
29. Pebody RG, Gay NJ, Giammanco A, et al. The seroepidemiology of Bordetella pertussis infection in Western Europe. *Epidemiol Infect* 2005; **133**(1): 159-71.
30. Launay O, Toneatti C, Bernede C, et al. Antibodies to tetanus, diphtheria and pertussis among healthy adults vaccinated according to the French vaccination recommendations. *Hum Vaccin* 2009; **5**(5): 341-6.
31. de Melker HE, Versteegh FG, Schellekens JF, Teunis PF, Kretzschmar M. The incidence of Bordetella pertussis infections estimated in the population from a combination of serological surveys. *J Infect* 2006; **53**(2): 106-13.
32. Ronn PF, Dalby T, Simonsen J, Jorgensen CS, Linneberg A, Krogfelt KA. Seroepidemiology of pertussis in a cross-sectional study of an adult general population in Denmark. *Epidemiol Infect* 2014; **142**(4): 729-37.
33. Cattaneo LA, Reed GW, Haase DH, Wills MJ, Edwards KM. The seroepidemiology of Bordetella pertussis infections: a study of persons ages 1-65 years. *J Infect Dis* 1996; **173**(5): 1256-9.
34. Strebel P, Nordin J, Edwards K, et al. Population-based incidence of pertussis among adolescents and adults, Minnesota, 1995-1996. *J Infect Dis* 2001; **183**(9): 1353-9.
35. Baughman AL, Bisgard KM, Edwards KM, et al. Establishment of diagnostic cutoff points for levels of serum antibodies to pertussis toxin, filamentous hemagglutinin, and fimbriae in adolescents and adults in the United States. *Clin Diagn Lab Immunol* 2004; **11**(6): 1045-53.
36. Scott S, van der Sande M, Faye-Joof T, et al. Seroprevalence of pertussis in the Gambia: evidence for continued circulation of bordetella pertussis despite high vaccination rates. *Pediatr Infect Dis J* 2015; **34**(4): 333-8.
37. Conde-Glez C, Lazcano-Ponce E, Rojas R, et al. Seroprevalence of Bordetella pertussis in the Mexican population: a cross-sectional study. *Epidemiol Infect* 2014; **142**(4): 706-13.
38. Mack A. Latin American Pertussis Workshop: Summary of Proceedings. 2019. https://www.sabin.org/sites/sabin.org/files/latin_american_pertussis_meeting_report_english_final.pdf (accessed July 16th 2021.
39. Statistics-Netherlands-CBS. Caribbean Netherlands; population, gender, age and country of birth. 2017. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/84712NED/table?ts=1612802577435 (accessed February 8th 2021.
40. Cutts FT, Hanson M. Seroepidemiology: an underused tool for designing and monitoring vaccination programmes in low- and middle-income countries. *Trop Med Int Health* 2016; **21**(9): 1086-98.

PART II

Maternal Tdap vaccination in a Public Health point-of-view

CHAPTER 9

Socio-psychological determinants of second trimester maternal pertussis vaccination acceptance in the Netherlands

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Abstract

Background

A maternal tetanus-diphtheria-and-acellular-pertussis (Tdap) vaccine is offered to all pregnant women in the Netherlands in their second trimester since December 2019. However, former studies solely investigated the socio-psychological factors that influence vaccine acceptance among pregnant women in the third trimester. We identified predicting factors for attitude, intention and acceptance of maternal Tdap vaccination during the second trimester of pregnancy.

Methods

As part of a large prospective cohort study, women early in pregnancy completed a questionnaire on determinants regarding acceptance of maternal Tdap vaccination between 20-24w of gestation. The vaccine was offered after completion of the questionnaire. A random forest model and Receiver Operating Characteristics (ROC) analyses were carried out to identify the factors most predictive for vaccine acceptance on the whole dataset, and also in sensitivity analysis on a subset reflecting the annual nationwide 70% vaccination uptake.

Results

Among 1158 participants who were offered a Tdap vaccination between 20-24w of gestation, 1098 (94.8%) accepted and 60 (5.2%) rejected the vaccine. Random forest analyses identified intention as most predictive for acceptance, followed by attitude towards vaccination, beliefs regarding safety, risk perception of severity of side effects, moral responsibility, beliefs regarding effectiveness and risk perception of susceptibility of side effects, with a sensitivity of 100% and a specificity of 40%, for which this combination could be improved by the ROC analysis to 82% and 67%, respectively. The sensitivity analysis yielded an order of predictors that generally corresponded with the initial model.

Conclusions

Intention, attitude, beliefs on safety and effectiveness, risk perception of side effects and moral responsibility were most predictive for maternal Tdap vaccine acceptance during the second trimester of pregnancy, in accordance with studies regarding third trimester vaccination. These should be discussed by healthcare professionals early in pregnancy to provide an informed choice towards vaccine acceptance.

Introduction

Pertussis is a highly contagious respiratory infectious disease caused mainly by *Bordetella pertussis*. Young infants are at risk of severe disease, which may lead to convulsions, encephalopathy or death.[1,2] *B. pertussis* may be readily transmitted to vulnerable infants as immunological protection is lacking before primary vaccinations.[3,4] These infants depend on maternal antibodies for protection against disease in the first months after birth, and therefore a growing number of countries have now implemented a maternal immunization strategy against pertussis.[5] Maternal vaccine-induced IgG antibodies are actively transferred across the placenta and provide infant protection against disease, until infants receive primary vaccinations.[6]

In 2015, the Health Council of the Netherlands advised to offer a pertussis vaccination to women during the third trimester of pregnancy.[7] Women could obtain a tetanus, diphtheria and acellular pertussis (Tdap) vaccination on their own initiative at municipal health services, general practitioner, midwife or obstetrician. Vaccine uptake increased rapidly in 2018 and 2019.[8] Later research demonstrated that term infants born to second trimester vaccinated mothers had higher antibody levels at birth than those of third trimester vaccinated mothers.[9] Even in preterm infants, antibody levels were higher after second trimester vaccination, which is postulated to be the result of a larger time interval between vaccination and delivery, providing a longer duration of transplacental antibody transfer.[10,11] Subsequently, several countries advised offering pregnant women the Tdap vaccination earlier throughout pregnancy.[12,13] After England had widened the time interval for vaccination at the earliest opportunity at 20 weeks of gestation, the uptake increased from an approximate 60 to 75%.[14] In the Netherlands, a maternal Tdap vaccination was included under the National Immunization Program (NIP) since December 2019, and is now offered free of charge to all Dutch pregnant women from 22 weeks of gestation. In 2021, vaccine uptake ranged around 70%.[15,16]

Many studies investigated the socio-psychological factors that might promote or hamper vaccine acceptance among pregnant women, showing that factors associated with maternal Tdap vaccination uptake were beliefs about vaccine effectiveness and safety,[17-20] attitude of their healthcare professional towards maternal Tdap immunization,[17,18,20-25] and logistical matters for obtaining the vaccine.[26] In relation to the timing throughout pregnancy, some studies suggested that women are less willing to accept a Tdap vaccination during their second trimester and prefer vaccination later throughout gestation.[27,28] However, these studies were conducted without the current knowledge that infants may benefit

from second trimester to a larger extent compared with third trimester Tdap vaccination. To the best of our knowledge, further information on socio-psychological determinants regarding Tdap vaccine acceptance during the second trimester of pregnancy remains unavailable.

This study aimed to fill the knowledge gap on socio-psychological factors associated with attitudes, intention and actual behavior towards Tdap vaccination acceptance in the second trimester of pregnancy. Identifying the factors that concern second trimester vaccine acceptance may guide antenatal care providers in optimizing communication and facilitating an informed choice regarding early Tdap vaccine administration. In addition, we assessed whether nulliparous and multiparous women differed in vaccine acceptance or in the determinants that may contribute to acceptance.

Methods

Design and setting

This study is part of a large prospective cohort study (PIMPI study) among pregnant women regarding acceptance, immunogenicity and reactogenicity of second trimester maternal Tdap vaccination. Full details of all study procedures were described previously.[29] Pregnant women of at least 18 years of age were recruited by their antenatal care provider before 20 weeks of gestation in the period of August 2019 throughout November 2021. Participants completed a questionnaire on determinants regarding acceptance of maternal Tdap vaccination in the second trimester of pregnancy.

The vaccine was administered free of charge by the antenatal care provider (midwife, obstetrician or OB-GYN resident) or at a youth healthcare center, after which the vaccination status was requested from the national vaccination registry. Participants were excluded if they were vaccinated before $20^{0/7}$ or after $24^{0/7}$ weeks of gestation. 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). All participants provided verbal and written informed consent.

Questionnaire

The online questionnaire covered behavioral determinants and beliefs that may underlie Tdap vaccination acceptance between 20 and 24 weeks of gestation. These were measured in theoretical constructs that consisted of single- or multiple-item 7-point Likert scales. An overview of constructs and internal consistency, the number of items, reliability and an example question for each

construct is presented in Table 1. Constructs were based on the Theory of Planned Behavior and the Health Belief Model.[30,31]

Intention was defined as an individual's readiness to perform certain behavior, i.e. whether or not accepting a maternal Tdap vaccination. Attitude, i.e. the assumed major predictor of intention, was defined as the degree to which the individual had a favorable or unfavorable evaluation of taking the vaccine.[30] Social norms included descriptive norms and injunctive norms. These norms reflected the behavior that women expect from pregnant women, from their antenatal care provider, or from other people who are important to them. Further constructs included in the questionnaire were: perceived risks of susceptibility and severity of disease; perceived risks of vaccine side effects in mother and child; beliefs about effectiveness, safety and several other aspects of maternal Tdap vaccination; decisional certainty; anticipated regret of vaccinating or not vaccinating; moral responsibility of vaccinating; fear of vaccinating or fear disease in the baby; and trust in the NIP and healthcare professionals. A full list of all individual constructs was presented in Table 1.

Socio-demographics were age, country of birth, education level, gravidity, parity, whether or not her lastborn child participated in the NIP (if parity ≥1) and the affiliation to certain beliefs. A similar study from before the enrollment of the maternal Tdap vaccination within the NIP in the Netherlands distinguished socio-psychological factors between women who recently delivered from a baby versus women without children. To illustrate any differences, we stratified between nulli- and multiparous women within our demographic variables. Questions within the questionnaire were based on the same study, from which the authors of this study aided in the development and evaluation of the questionnaire.

Statistical analysis

R software 4.0.4 was used for analyses. Items within the same underlying theoretical construct were averaged into one single construct in case internal consistency was sufficiently high (Cronbach's alpha $\alpha \geq .60$). Spearman's correlation test was used to explore univariate associations between intention and social cognitive determinants, underlying beliefs possible barriers and facilitators and the abovementioned socio-demographic affiliation to beliefs. We adopted Cohen's interpretation of Spearman's effect sizes, i.e. that a correlation of 0.10-0.23 indicates a small effect, one of 0.24-0.36 a moderate effect, and one ≥0.37 a large effect.[32]

Next, a random forest model was constructed to assess the ability of the questionnaire to predict vaccine acceptance and to identify major predictive

constructs.[33] The accuracy of the model was measured as the probability of predicting correctly whether a newly sampled individual would accept vaccination based on the individual's questionnaire response, or equivalently as one minus that probability, called the probability of misclassification (pmc).

In order to strengthen the initial analysis, an ROC (Receiver Operating Characteristics) analysis of the prediction of acceptance was conducted. While the goal of the basic analysis was minimizing the pmc, the model predicts acceptance if the individual's ratio of the probability of acceptance to the probability of rejection is ≥1 and rejection otherwise. Replacing 1 by a 'varying threshold' (c) gives a set of predictors, each with its own performance characteristics. The most desirable performance is found when the value of c yields the most balanced estimates of sensitivity and specificity. This type of analysis is especially useful when, as in our case, acceptance is very high in the population, causing the initial algorithm to minimize the pmc at the cost of a very low specificity. In this situation, the ROC analysis balances specificity and sensitivity at a high level without greatly increasing the pmc, hence to enhance the predictive value of the data as a whole.

In a sensitivity analysis designed to assess the influence of the prevalence of acceptance on its performance statistics, the initial prediction analysis was carried out on a subset of the data on the 60 rejectors in the whole sample and a random selection of 140 acceptors, reflecting the nationwide vaccine coverage 70%. By thus artificially sub-sampling the population of acceptors, we assessed whether or not this sensitivity analysis yielded comparable results with the initial analysis, thereby increasing specificity as the numbers of acceptors and rejectors were more equally distributed.

Lastly, we calculated proportions of vaccine acceptance and means with corresponding standard deviations (sd) for socio-psychological constructs and stratified for women who did or did not already have children. Basic descriptive statistic tests with adjustment for multiple comparisons were used in order to assess whether acceptance and underlying constructs differed between both groups.

Results

Study population characteristics

1377 participants completed the questionnaire, of whom 1158 (84.1%) enrolled for follow-up after vaccine acceptance or rejection within the correct time interval between $20^{0/7}$ and $24^{0/7}$ weeks of gestation. In total, 1098 women (94.8%) accepted and 60 (5.2%) rejected the vaccine. Demographical factors, e.g. country of birth, education level and type of antenatal care, were similar between nulliparous and

Table 1. Internal consistency and example questions of theoretical constructs.

Theoretical construct	Number of items	Reliability [a]	Example question	Answer
Intention (1=low - 7=high)	3	α=0.96	I would be willing to get vaccinated against pertussis during pregnancy.	1 = completely disagree; 7 = completely agree
Attitude (1=negative - 7=positive)	3	α=0.91	I think vaccination against pertussis during pregnancy is:	1 = not important at all; 7 = very important
Descriptive norm (1=low - 7=high)	1	NA	I think that most pregnant women will get vaccinated against pertussis during pregnancy.	1 = completely disagree; 7 = completely agree
Injunctive norm antenatal care provider (1=low - 7=high)	1	NA	I think that my midwife or gynecologist will appreciate if I get vaccinated against pertussis during pregnancy.	1 = completely disagree; 7 = completely agree
Injunctive norm other important people (1=low - 7=high)	1	NA	I think that the people who are important to me will appreciate if I get vaccinated against pertussis during pregnancy.	1 = completely disagree; 7 = completely agree
Risk perception of pertussis susceptibility in baby (1=low - 7=high)	1	NA	Imagine you do not get vaccinated against pertussis during pregnancy, what do you think the chance is that your baby gets pertussis?	1 = very small; 7 = very large

multiparous women, except for pregnancy related demographics (Table 2).

Table 1. Continued

Theoretical construct	Number of items	Reliability [a]	Example question	Answer
Risk perception of pertussis severity in baby (1=low - 7=high)	1	NA	How severe is pertussis in babies according to you?	1 = not severe at all; 7 = very severe
Risk perception susceptibility of side effects vaccine (1=low - 7=high)[b]	3	α=0.72	Imagine you get vaccinated against pertussis during pregnancy, what do you think the chance is that your baby gets side effects?	1 = very small; 7 = very large
Risk perception severity of side effects vaccine (1=low - 7=high)[b]	2	α=0.77	How severe are the side effects of pertussis vaccination during pregnancy for the baby?	1 = not severe at all; 7 = very severe
Belief safety (1=unsafe - 7=safe)	9	α=0.86	I think that vaccinating against pertussis during pregnancy is safe for the baby.	1 = completely disagree; 7 = completely agree
Belief effectiveness (1=low - 7=high)	3	α=0.68	I think that vaccinating against pertussis during pregnancy results in fewer pertussis infections in babies.	1 = completely disagree; 7 = completely agree
Belief effectiveness having pertussis (1=low - 7=high)	2	α=0.85	I think that going through pertussis is positive for my baby.	1 = completely disagree; 7 = completely agree
Belief protection vaccines (1=low - 7=high)	1	NA	I think that vaccinating does not provide sufficient protection against infectious diseases.	1 = completely disagree; 7 = completely agree [c]

Table 1. Continued

Theoretical construct	Number of items	Reliability [a]	Example question	Answer
Belief alternative (1=low - 7=high)	1	NA	I think there is a good alternative for a pertussis vaccination during pregnancy.	1 = completely disagree; 7 = completely agree
Decisional certainty (1=uncertain - 7=certain)	2	α=0.86	Deciding whether to get vaccinated against pertussis during my pregnancy took me a long time to think about.	1 = completely disagree; 7 = completely agree [c]
Anticipated regret not vaccinating (1=low - 7=high)	1	NA	Imagine you do not get vaccinated against pertussis during pregnancy and your baby gets pertussis, how much regret would you feel about your decision not to get vaccinated?	1 = no regret at all; 7 = a lot of regret
Anticipated regret vaccinating (1=low - 7=high)	1	NA	Imagine you get vaccinated against pertussis during pregnancy and your baby gets side effects, how much regret would you feel about your decision to get vaccinated?	1 = no regret at all; 7 = a lot of regret
Moral responsibility (1=low - 7=high)	2	α=0.69	I think that it is my responsibility as a pregnant woman to get vaccinated against pertussis during pregnancy to protect my baby.	1 = completely disagree; 7 = completely agree

Table 1. Continued

Theoretical construct	Number of items	Reliability [a]	Example question	Answer
Fear vaccinating (1=low - 7=high)	1	NA	When I think about getting vaccinated during pregnancy I feel:	1 = no fear at all; 7 = very much fear
Fear disease (1=low - 7=high)	1	NA	When I think about my baby getting pertussis I feel:	1 = no fear at all; 7 = very much fear
Trust in NIP and healthcare professionals (1=low - 7=high)	3	α=0.87	How much trust do you have in information you get about pertussis vaccination during pregnancy from your midwife or gynecologist?	1 = no trust at all; 7 = a lot of trust
Distrust pharmaceutical industry (1=low - 7=high)	1	NA	I think that the pertussis vaccination is offered to pregnant women so that the pharmaceutical industry can make money from it.	1 = completely disagree; 7 = completely agree
Social pressure (1=low - 7=high)	1	NA	I feel pressured by others when making a choice about vaccinating against pertussis during my pregnancy.	1 = completely disagree; 7 = completely agree
Benefit of one fewer infant vaccine (1=not beneficial - 7=beneficial)[d]	1	NA	I appreciate it when my baby can start the vaccinations later and needs one fewer vaccine, because I get vaccinated during pregnancy.	1 = completely disagree; 7 = completely agree

Table 1. Continued

Theoretical construct	Number of items	Reliability [a]	Example question	Answer
Barrier of combined vaccine components (1=low - 7=high)	1	NA	I do not appreciate that the pertussis vaccination is a combination vaccine, which means I am also vaccinated against other infections (diphtheria and tetanus).	1 = completely disagree; 7 = completely agree

[a] No reliability was applicable for constructs that consist of a single item (NA). [b] Constructs about side effects covers questions about both mother and infant. [c] The low and high scores (1 to 7) of this example question were reversed. [d] According to the Dutch vaccination schedule, infants of mother's who were vaccinated during pregnancy receive one vaccine fewer than infants of unvaccinated mothers.

Table 2. Baseline characteristics and socio-psychological constructs of pregnant women stratified for recruitment strategy.

Demographics	**Nulliparous women n=494 (42.7%)**	**Multiparous women n=664 (57.3%)**	**p-value**
Age in years; mean (sd)	30.8 (4.4)	32.9 (3.8)	<0.001*
Country of birth; n (%)			0.327
The Netherlands	448 (90.7)	614 (92.5)	
Other	46 (9.3)	50 (7.5)	
Education level; n (%)[a]			0.890
High	330 (66.8)	447 (67.3)	
Middle	141 (28.5)	183 (27.6)	
Low	23 (4.7)	34 (5.1)	
Has been pregnant before; n (%)			<0.001*
Yes	104 (21.1)	660 (99.4)	
No	390 (78.9)	4 (0.6)[b]	
Antenatal care provider; n (%)			0.680
Midwife in primary care facility	317 (64.2)	407 (61.3)	
Midwife in hospital	58 (11.7)	84 (12.7)	
OB-GYN resident	7 (1.4)	14 (2.1)	
Gynecologist	112 (22.7)	159 (23.9)	
Participation to the NIP by youngest child; n (%)			NA
Received all vaccinations	NA	619 (93.2)	
Received some vaccinations	NA	14 (2.1)	
Received no vaccination	NA	18 (2.7)	
Unknown	NA	3 (0.5)	
No answer	NA	10 (1.5)	
Affiliation to beliefs (1=no affiliation - 7=strong affiliation); mean (sd)			
Religion	2.0 (1.8)	2.1 (1.9)	0.356
Homeopathy	1.9 (1.3)	1.9 (1.4)	0.652
Natural cure	1.9 (1.4)	1.8 (1.4)	0.343
Anthroposophy	1.4 (1.0)	1.5 (1.1)	0.484

Acceptance and Socio-psychological variables			
Vaccine acceptance; n (%)			0.230
Yes	476 (96.4)	622 (93.7)	
No	18 (3.6)	42 (6.3)	
Intention (1=low; 7=high); mean (sd)	6.5 (1.0)	6.4 (1.1)	0.912
Attitude (1=negative; 7=positive); mean (sd)	5.7 (1.0)	5.7 (1.1)	0.506
Descriptive norm (1=low; 7=high); mean (sd)	4.9 (1.4)	4.8 (1.4)	0.230
Injunctive norm antenatal care provider (1=low; 7=high); mean (sd)	4.8 (1.8)	4.6 (1.9)	0.230
Injunctive norm other important people (1=low; 7=high); mean (sd)	5.0 (1.6)	4.9 (1.7)	0.506
Risk perception of pertussis susceptibility in baby (1=low; 7=high); mean (sd)	3.1 (1.3)	2.9 (1.3)	0.039*
Risk perception of pertussis severity in baby (1=low; 7=high); mean (sd)	5.8 (1.2)	5.9 (1.2)	0.230
Risk perception susceptibility of side effects vaccine (1=low; 7=high); mean (sd)	1.9 (0.8)	1.7 (0.9)	0.052
Risk perception severity of side effects vaccine (1=low; 7=high); mean (sd)	1.7 (0.9)	1.6 (0.9)	0.140
Belief safety (1=unsafe; 7=safe); mean (sd)	5.7 (0.9)	5.7 (1.0)	0.697
Belief effectiveness (1=low; 7=high); mean (sd)	6.0 (0.9)	6.0 (1.1)	0.931
Belief effectiveness having pertussis (1=low; 7=high); mean (sd)	1.6 (1.3)	1.6 (1.3)	0.931
Belief protection vaccines (1=low; 7=high); mean (sd)	6.0 (1.2)	6.1 (1.2)	0.497
Belief alternative (1=low; 7=high); mean (sd)	1.8 (1.1)	1.9 (1.4)	0.230

Decisional certainty (1=uncertain; 7=certain); mean (sd)	5.3 (1.7)	5.3 (1.7)	0.797
Anticipated regret not vaccinating (1=low; 7=high); mean (sd)	6.3 (1.3)	6.2 (1.3)	0.861
Anticipated regret vaccinating (1=low; 7=high); mean (sd)	4.4 (1.7)	4.4 (1.7)	0.320
Moral responsibility (1=low; 7=high); mean (sd)	5.4 (1.3)	5.2 (1.5)	0.230
Fear vaccinating (1=low; 7=high); mean (sd)	2.4 (1.7)	2.3 (1.6)	0.394
Fear disease (1=low; 7=high); mean (sd)	6.1 (1.1)	6.2 (1.2)	0.230
Trust in NIP and healthcare professionals (1=low; 7=high); mean (sd)	6.0 (0.9)	6.0 (1.0)	0.589
Distrust pharmaceutical industry (1=low; 7=high); mean (sd)	1.8 (1.2)	1.7 (1.1)	0.374
Social pressure (1=low; 7=high); mean (sd)	1.4 (1.0)	1.4 (0.9)	0.598
Benefit of one fewer infant vaccine (1=not beneficial; 7=beneficial); mean (sd)	5.9 (1.4)	5.7 (1.6)	0.140
Barrier of combined vaccine components (1=low; 7=high); mean (sd)	2.5 (1.8)	3.0 (1.9)	0.026*

[a] Maternal education level categories, i.e. Low = no education, primary school, pre-vocational education (VMBO) and lower general education (MAVO/VMBO-TL). Middle = intermediate vocational education (MBO), higher/senior vocational education (HAVO) and pre-university education (VWO/Gymnasium); high = higher professional education (HBO), university BSc., university MSc. and doctorate. [b] Partner carried previous pregnancy. * Significance level $p<0.05$

Constructs and correlations with intention towards vaccine acceptance

All items within the multi-item theoretical constructs were considered sufficiently consistent to each other (Cronbach's α ranged between 0.68-0.96) (Table 1). Constructs with a large effect on intention (Spearman's $r\geq0.37$) were attitude ($r=0.66$), belief safety ($r=0.61$), belief of effectiveness ($r=0.55$), trust in NIP and healthcare professionals ($r=0.55$), moral responsibility ($r=0.51$), risk perception susceptibility of side effects ($r=-0.49$), risk perception severity of side

effects (r=-0.48), decisional certainty (r=0.44) and fear of vaccination (r=-0.40). Visualization of all associations with intention and other constructs were presented in Supplementary figure 1.

Factors associated with acceptance of second trimester maternal Tdap vaccination

Figure 1A shows the variable importance of all the predictors included in the random forest model that predicts vaccine acceptance. While intention was most predictive for acceptance, other predictors highly associated with acceptance were attitude towards vaccination, belief safety, risk perception of severity of side effects, moral responsibility, belief effectiveness and risk perception of susceptibility of side effects. The model holds a pmc of 4%, a sensitivity of 100% (probability of correctly detecting vaccine acceptors) and a specificity of 40% (probability of correctly detecting vaccine rejectors). The ROC curve in Figure 1B implies that if vaccine acceptance and rejection reflected nationwide coverage, the combination of sensitivity and specificity could more balanced to 82% and 67%, respectively, at the cost of increasing the pmc to 19%. The area under the curve had a proportion of 0.78.

The sensitivity analysis based on the artificial dataset of the 60 vaccine rejectors and a random selection of 140 acceptors, reflecting Dutch nationwide vaccine coverage of 70%, yielded an order of variable importance that generally agreed with the initial ranking (Supplementary figure 2). The most remarkable difference between the models is that the variable importance of decisional certainty showed a two-fold increase in the sensitivity analysis compared with the initial model. Less remarkable differences were found for trust in NIP and healthcare professionals and for anticipated regret of vaccinating. As expected, the overall specificity within the artificial dataset increased from 40% to 55% at a marginal decrease of sensitivity to 96%.

Differences between nulliparous and multiparous women

Vaccine acceptance was not found to be different between nulliparous and multiparous women (p=0.230). Nulliparous women had a significantly higher mean score for risk perception of pertussis susceptibility in their baby (3.1 vs 2.9, p=0.039), and a lower mean score for feeling a barrier in being vaccinated against combined vaccine components (2.5 vs 3.0, p=0.026) (Table 2). Risk perception of susceptibility to side effects of the vaccine seemed to be marginally different between the groups (p=0.052).

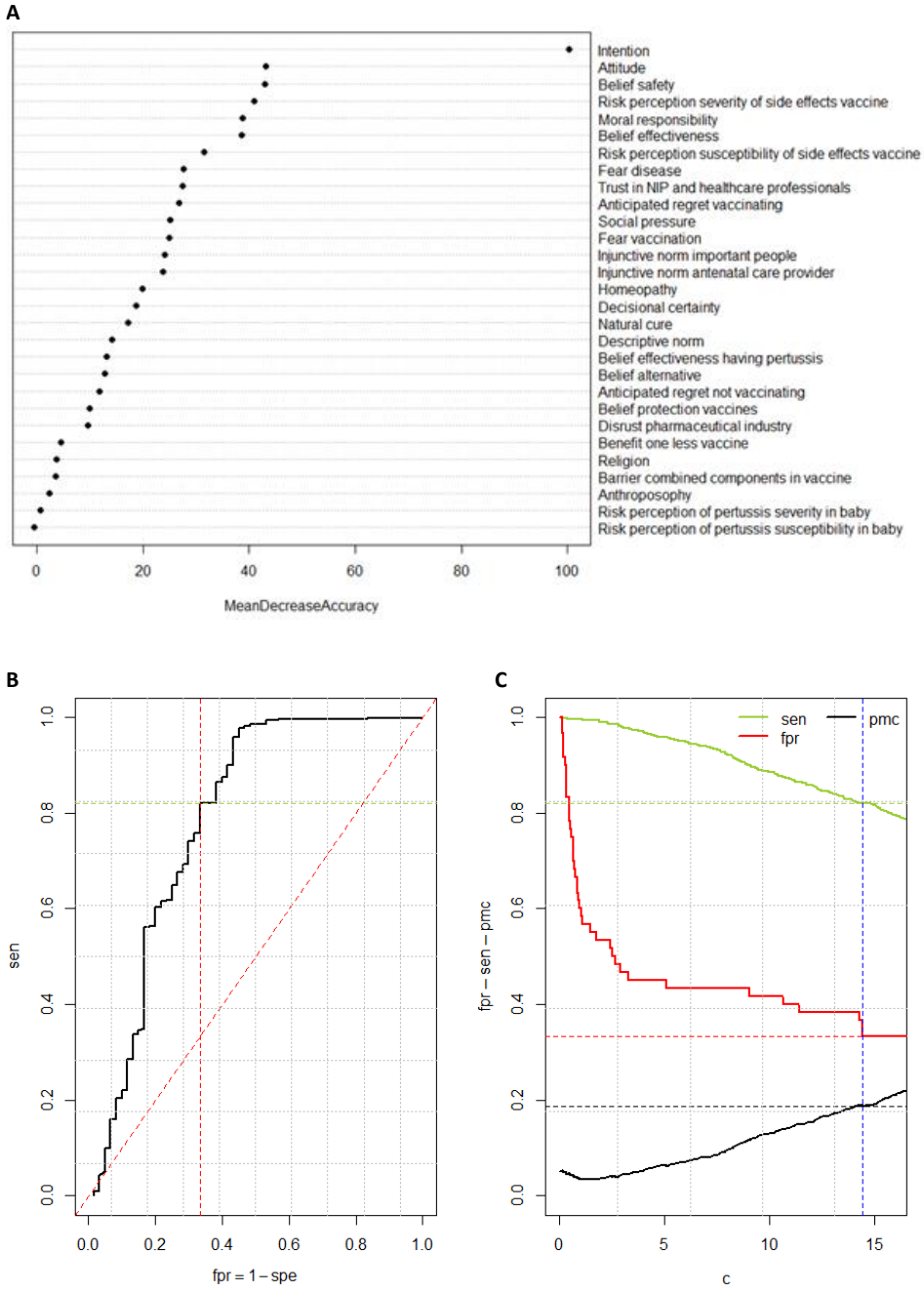


Figure 1. Random forest analysis and Receiver Operating Characteristics (ROC) curve. Panel A: Relative importance of the constructs used to predict acceptance of vaccination in a random forest model with pmc (probability of misclassification) of 4%, sen (sensitivity) of 100% and spe (specificity) of 40%. The greater the mean decrease in accuracy, the more predictive the construct. Panels B and C: Results of

the ROC (Receiver Operating Characteristics) analysis. The dashed blue line indicates the optimal cut-off value for the ratio of acceptance versus rejection at which the model assigns a positive prediction (c) with the highest combination sensitivity (0.82), specificity (0.67=1-false positive rate (fpr)) and the lowest probability of misclassification (0.19). The area under the ROC curve, 0.78, is often used as an indicator of the predictive value of the data as a whole.

Discussion

This study identified the socio-psychological factors that were associated with acceptance of second trimester maternal Tdap vaccination among pregnant women. We found that intention towards vaccination was most predictive for vaccine acceptance, followed by attitude, belief in the safety and the effectiveness of the vaccine, lower risk perception of severity and susceptibility of vaccination side effects and feeling a moral responsibility to accept. Sensitivity analysis among a sub-sample of 60 vaccine rejectors and a random selection of 140 acceptors yielded an order of predictive variables that generally corresponded with the initial analysis. No differences in attitude or intention towards vaccination, or actual vaccine acceptance were found between nulliparous and multiparous women.

Our findings were in accordance with a similar study that assessed determinants towards third trimester maternal Tdap vaccine acceptance by pregnant women in the Netherlands.[34] In line with our results, the authors concluded that attitude, moral responsibility, beliefs about safety and beliefs about vaccine effectiveness were shown most predictive for vaccination intention (actual acceptance was not assessed). Despite the similarity in predicting factors regarding vaccine acceptance between both studies, absolute means of the four major predictors were lower compared with our study (attitude 4.2 vs 5.7, moral responsibility 3.9 vs 5.4, belief safety 3.9 vs 5.7 and belief effectiveness 5.1 vs 6.0, respectively). We believe that these differences may lie in the fact that the previous study was conducted in April 2017, i.e. far before the introduction of maternal Tdap vaccination in the Netherlands. Now that the vaccination is implemented in the Netherlands, pregnant women's awareness on the vaccination may have contributed to overall positive opinions on acceptance, affecting our results. Secondly, our study population holds an approximate 95% acceptance rate, while our nationwide vaccine coverage is approximately 70%,[15,16] and therefore, our results may be more optimistic than in real life. Nevertheless, our findings emphasize that the same predicting factors apply to acceptance of maternal vaccination earlier throughout pregnancy, even though previous studies suggested that women would prefer vaccination in their third trimester, [27,28] which was stated before we had knowledge on the benefits of second trimester vaccination. Therefore, we encourage the relevant healthcare professionals to promote

maternal Tdap vaccination by supporting women about the abovementioned determinants, preferably during the early-second trimester of pregnancy.

Intention, attitude, vaccine safety and effectiveness were also predictive for vaccine acceptance in other studies.[17-20,34]When it comes to pregnant women feeling moral responsibility to accept the vaccine, the norm-activation theory suggests that moral norms influence behavior when pregnant women are aware of the consequences of accepting or rejecting the vaccine.[35,36] We found this theory applicable to our findings because moral responsibility correlated well to its successive variables, with a strong or moderate effect size for anticipated regret not vaccinating (r=0.45), risk perception severity of side effects vaccine (r=-0.35), risk perception susceptibility of side effects vaccine (r=-0.29), fear of disease (r=0.28) and the benefit of one fewer infant vaccination (r=0.24). Making women aware of these consequences contributes to the process of making a well-considered decision whether or not to vaccinate during pregnancy.

Nulliparous women had a significantly higher mean score for risk perception of pertussis susceptibility in their baby, and they were less concerned that the vaccine contained multiple components. These variables, however, were two of the least predictive determinants for vaccine acceptance, so we do not expect any serious consequences for vaccine uptake as a result of these differences. Nevertheless, elevated risk perception of infant susceptibility for pertussis in nulliparous women suggests that women were more concerned about the vulnerability of their first unborn infant. A previous study suggested that elevated risk perception of pertussis (both susceptibility and severity) was associated with attitude towards vaccination, but not intention.[34] This is in line with our results as we found small to moderate correlations of risk perception to attitude (r=0.13 for susceptibility and r=0.27 for severity) but lower correlations to vaccination intention. While the previous study did not assess actual vaccine acceptance, and risk perception of disease was not predictive for vaccine acceptance in our study, we encourage healthcare professionals to stick to the most relevant determinants during vaccine promotion, e.g. safety, effectiveness and the abovementioned consequences of behavior.

This study has limitations. As mentioned before, 94.8% of all study participants accepted the Tdap vaccination, while current national vaccine coverage ranges around 70%.[15,16] Therefore, our results may be more optimistic than in real life. The difference can be partially explained because at the end of the questionnaire, many participants voluntarily commented that participation in this study yielded free vaccination (before December 2019) and the ability to obtain the vaccine without making a separate appointment for vaccination, which suggests selection bias. The

low number of vaccine rejectors in our study has most likely resulted into low specificity of our random forest model, which we aimed to compensate for by putting the c-value appropriately high, thereby decreasing the likeliness of the model to predict vaccine acceptance. This means that sensitivity and specificity could be more balanced, even though the number of vaccine rejectors was low. Even though specificity remained low, probably due to the low number of vaccine rejectors, our sensitivity analysis among 60 vaccine rejectors and 140 acceptors speaks for the generalizability of our model as the generally agreed to the initial model for most variables, at least for the part of the population that accepts maternal Tdap vaccination. Another limitation is that our results may not be completely generalizable to a population of pregnant women within a few years of time, as a random forest model is unable to provide an estimate of the strength of an association, nor indicates a causal pathway. Our purpose in this work was to identify the main patterns that predict an individual's vaccination status from its personal characteristics. In order to explore possible themes that may arise before, during, or after the decision making process among pregnant women, we suggest that follow-up studies should be performed in a more qualitative manner preferred over statistical models. Decisional certainty showed the most remarkable difference between the models, followed by trust in NIP and healthcare professionals and anticipated regret. Decisional certainty however is difficult to interpret, as high certainty on any successive decision does not necessarily mean that one would accept or reject, and vice versa. Overall, the low specificity and high sensitivity together show that it remains difficult to identify the factors that predict vaccine rejection, and our results speak predominantly for the prediction of vaccine acceptance as opposed to rejection. Finally, the proportions of participants who accepted a Tdap vaccine before versus after the end of February 2020 were 98% vs 93%, respectively. It could be that the COVID-19 vaccination has contributed to this (small) difference. However, we believe that the introduction of free maternal Tdap vaccination within the NIP (December 2019) contained the largest influence on the reduction of the vaccine acceptance rate, since the benefit of free vaccination within participation in our study was no longer applicable from this moment onwards. Since the abovementioned dates are so close together, we cannot distinguish whether or not vaccine acceptance was influenced by this phenomenon and the COVID-19 situation.

Conclusion

In accordance with other studies assessing third trimester maternal Tdap vaccine acceptance, acceptance during the second trimester of pregnancy can be

predicted by intention and attitude towards vaccination, belief in the safety and the effectiveness of the vaccine, the risk perceptions to the severity and susceptibility of vaccination side effects and feeling moral responsibility to take the vaccine. These predictors should be discussed early in pregnancy by healthcare professionals for providing women an informed choice regarding vaccine acceptance.

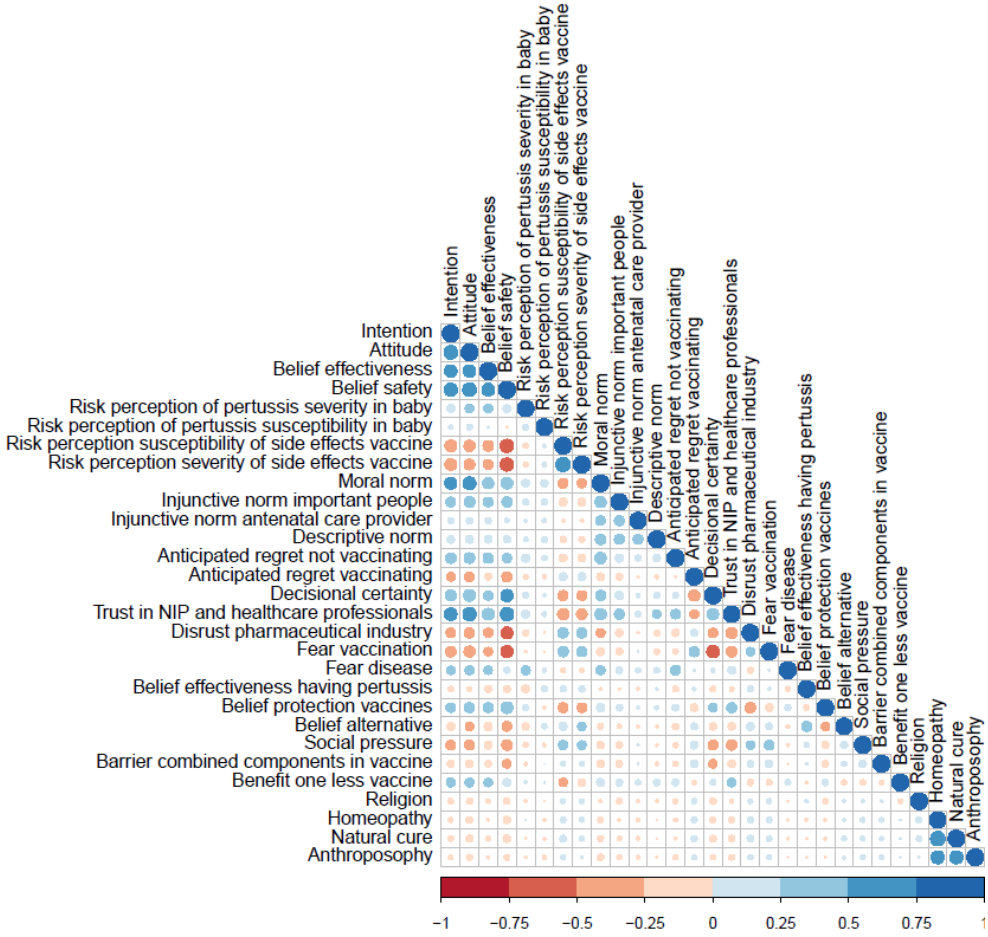
Supplementary materials

Supplementary table 1. Means and standard deviations of socio-psychological constructs stratified vaccine acceptors and rejectors.

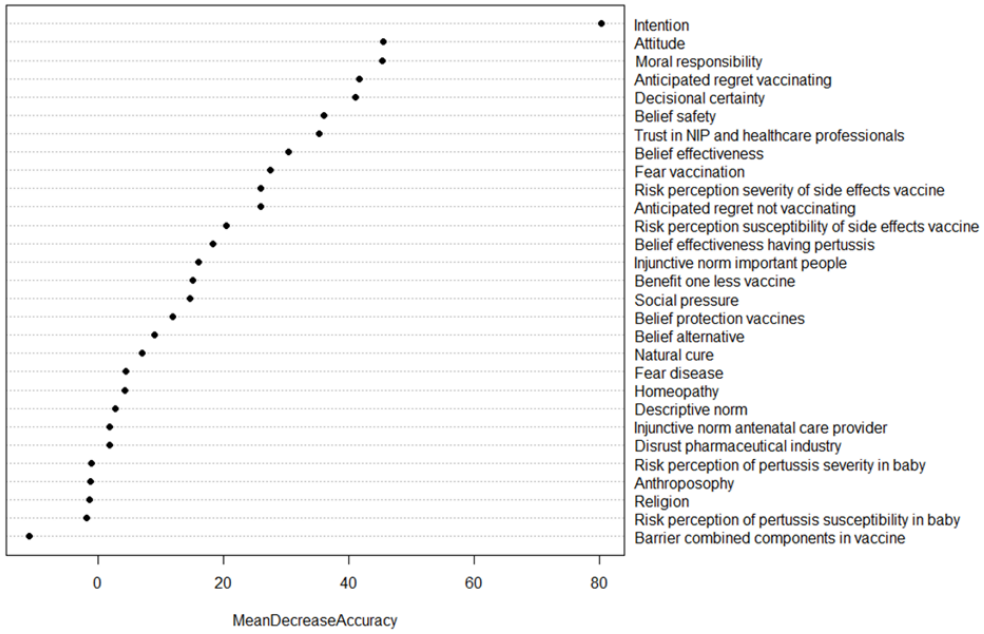
Acceptance and Socio-psychological variables	Vaccine acceptors n=1098 (94.8%)	Vaccine rejectors n=60 (5.2%)	p-value
Intention (1=low; 7=high); mean (sd)	6.6 (0.7)	4.2 (2.5)	<0.001*
Attitude (1=negative; 7=positive); mean (sd)	5.8 (1.0)	4.3 (1.6)	<0.001*
Descriptive norm (1=low; 7=high); mean (sd)	4.9 (1.4)	4.2 (1.9)	<0.001*
Injunctive norm antenatal care provider (1=low; 7=high); mean (sd)	4.7 (1.9)	4.1 (2.1)	0.008*
Injunctive norm other important people (1=low; 7=high); mean (sd)	5.0 (1.6)	3.5 (2.1)	<0.001*
Risk perception of pertussis susceptibility in baby (1=low; 7=high); mean (sd)	3.0 (1.3)	2.6 (1.3)	0.037*
Risk perception of pertussis severity in baby (1=low; 7=high); mean (sd)	5.9 (1.2)	5.2 (1.7)	<0.001*
Risk perception susceptibility of side effects vaccine (1=low; 7=high); mean (sd)	1.7 (0.7)	2.8 (1.6)	<0.001*
Risk perception severity of side effects vaccine (1=low; 7=high); mean (sd)	1.6 (0.8)	2.6 (1.5)	<0.001*
Belief safety (1=unsafe; 7=safe); mean (sd)	3.0 (1.3)	2.6 (1.3)	0.037*
Belief effectiveness (1=low; 7=high); mean (sd)	6.1 (0.9)	4.7 (1.7)	<0.001*
Belief effectiveness having pertussis (1=low; 7=high); mean (sd)	1.6 (1.3)	2.0 (1.5)	0.006*
Belief protection vaccines (1=low; 7=high); mean (sd)	6.1 (1.1)	5.1 (1.7)	<0.001*
Belief alternative (1=low; 7=high); mean (sd)	1.8 (1.3)	2.5 (1.4)	<0.001*

Decisional certainty (1=uncertain; 7=certain); mean (sd)	5.4 (1.7)	4.1 (2.4)	<0.001*
Anticipated regret not vaccinating (1=low; 7=high); mean (sd)	6.3 (1.2)	4.7 (2.2)	<0.001*
Anticipated regret vaccinating (1=low; 7=high); mean (sd)	4.3 (1.7)	5.3 (2.0)	<0.001*
Moral responsibility (1=low; 7=high); mean (sd)	5.4 (1.3)	3.8 (2.1)	<0.001*
Fear vaccinating (1=low; 7=high); mean (sd)	2.3 (1.6)	3.4 (2.2)	<0.001*
Fear disease (1=low; 7=high); mean (sd)	6.2 (1.1)	5.6 (1.8)	<0.001*
Trust in NIP and healthcare professionals (1=low; 7=high); mean (sd)	6.1 (0.9)	4.9 (1.5)	<0.001*
Distrust pharmaceutical industry (1=low; 7=high); mean (sd)	1.7 (1.1)	2.6 (1.9)	<0.001*
Social pressure (1=low; 7=high); mean (sd)	1.3 (0.9)	2.0 (1.6)	<0.001*
Benefit of one fewer infant vaccine (1=not beneficial; 7=beneficial); mean (sd)	5.9 (1.5)	4.9 (2.2)	<0.001*
Barrier of combined vaccine components (1=low; 7=high); mean (sd)	2.8 (1.9)	3.5 (2.2)	0.007*

*significance $p<0.05$.



Supplementary figure 1. Construct correlations. Correlations represented in blue if positively associated with corresponding predictor variable, and red otherwise. Spearman's effect size was considered small if r=0.10-0.23, moderate if r=0.24-0.36 and large r≥0.37, even so if the effect size was negative. Answers were measured on a Likert scale ranging from 1 to 7.



Supplementary figure 2. Random forest analysis among 60 vaccine rejectors and a randomly selected 140 acceptors, reflecting Dutch nationwide vaccine coverage of 70%. Random forest analysis indicating the strength of predictors' association with vaccine acceptance by a sensitivity of 0.96 and specificity of 0.55. The model shows the mean decrease in accuracy if the corresponding predictor was dropped from model.

References

1. van der Maas NA, van Aerde K, Bont LJ, Bekker MN, Rots N, de Melker HE. [Infection prevention in newborns through maternal vaccination: current insights and developments]. *Ned Tijdschr Geneeskd* 2016; **160**: D411.
2. Vegelin AL, van Vught AJ, Wolfs TF, Kimpen JL, Geelen SP. [Pertussis in young infants]. *Ned Tijdschr Geneeskd* 1998; **142**(49): 2657-60.
3. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014; **384**(9953): 1521-8.
4. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. *Clin Infect Dis* 2017; **64**(1): 3-8.
5. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. *Emerg Infect Dis* 2000; **6**(4): 348-57.
6. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; **36**(5): 248-55.
7. Dossier vaccinatie tegen kinkhoest: doel en strategie. 2015. https://www.gezondheidsraad.nl/documenten/adviezen/2015/12/02/vaccinatie-kinkhoest-doel-en-strategie.
8. Schurink-van 't Klooster TM, de Melker HE. The National Immunisation Programme in the Netherlands - Surveillance en Developments in 2019-2020, 2020.
9. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *Clin Infect Dis* 2016; **62**(7): 829-36.
10. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization. *Clin Infect Dis* 2017; **64**(8): 1129-32.
11. Maertens K, Orije MRP, Herzog SA, et al. Pertussis immunization during pregnancy: assessment of the role of maternal antibodies on immune responses in term and preterm born infants. *Clin Infect Dis* 2021.
12. Amirthalingam G, Brown CS, Campbell H, Chand MA, Fry NK. New Public Health England guidelines for managing pertussis in England. *J Infect* 2017; **74**(2): 202-4.
13. Vaccine schedules in all countries in the EU/EEA. https://vaccine-schedule.ecdc.europa.eu/.
14. Pertussis vaccination programme for pregnant women update: vaccine coverage in England, April to June 2018: Public Health England, 2018.
15. Pluijmaekers AJM, de Melker HE. The National Immunisation Programme in the Netherlands: Surveillance and Developments in 2020-2021: National Institute for Public Health and the Environment, 2021.
16. van Lier EAGO, P.J.; Giesbers, H.; van Vliet, J.A.; Hament, J-A.; Drijfhout, I.H.; Zonnenberg-Hoff, I.F.; de Melker, H.E. Vaccination Coverage and Annual Report National Immunisation Programme Netherlands 2020 [in Dutch: Vaccinatiegraad en Jaarverslag Rijksvaccinatieprogramma Nederland 2020], 2021.
17. Varan AK, Esteves-Jaramillo A, Richardson V, Esparza-Aguilar M, Cervantes-Powell P, Omer SB. Intention to accept Bordetella pertussis booster vaccine during pregnancy in Mexico City. *Vaccine* 2014; **32**(7): 785-92.
18. Hill L, Burrell B, Walls T. Factors influencing women's decisions about having the pertussis-containing vaccine during pregnancy. *J Prim Health Care* 2018; **10**(1): 62-7.
19. Hayles EH, Cooper SC, Sinn J, Wood N, Leask J, Skinner SR. Pertussis vaccination coverage among Australian women prior to childbirth in the cocooning era: a two-hospital, cross-sectional survey, 2010 to 2013. *Aust N Z J Obstet Gynaecol* 2016; **56**(2): 185-91.
20. Ko HS, Jo YS, Kim YH, et al. Knowledge and Acceptability about Adult Pertussis Immunization in Korean Women of Childbearing Age. *Yonsei Med J* 2015; **56**(4): 1071-8.
21. Winslade CG, Heffernan CM, Atchison CJ. Experiences and perspectives of mothers of the pertussis vaccination programme in London. *Public Health* 2017; **146**: 10-4.
22. McQuaid F, Jones C, Stevens Z, et al. Factors influencing women's attitudes towards antenatal vaccines, group B Streptococcus and clinical trial participation in pregnancy: an online survey. *BMJ Open* 2016; **6**(4): e010790.

23. O'Shea A, Cleary B, McEntee E, et al. To vaccinate or not to vaccinate? Women's perception of vaccination in pregnancy: a qualitative study. *BJGP Open* 2018; **2**(2): bjgpopen18X101457.
24. Bodeker B, Walter D, Reiter S, Wichmann O. Cross-sectional study on factors associated with influenza vaccine uptake and pertussis vaccination status among pregnant women in Germany. *Vaccine* 2014; **32**(33): 4131-9.
25. Laenen J, Roelants M, Devlieger R, Vandermeulen C. Influenza and pertussis vaccination coverage in pregnant women. *Vaccine* 2015; **33**(18): 2125-31.
26. Campbell H VHA, Bedford H, Craig L, Yeowell A-L, Green D, Yarwood J, Ramsay M, Amirthalingam G. Attitudes to immunisation in pregnancy among women in the UK targeted by such programmes. *British Journal of Midwifery* 2015; **Vol 23, No 8**.
27. van Lier A, Steens A, Ferreira JA, van der Maas NA, de Melker HE. Acceptance of vaccination during pregnancy: experience with 2009 influenza A (H1N1) in the Netherlands. *Vaccine* 2012; **30**(18): 2892-9.
28. Healy CM, Rench MA, Montesinos DP, Ng N, Swaim LS. Knowledge and attitiudes of pregnant women and their providers towards recommendations for immunization during pregnancy. *Vaccine* 2015; **33**(41): 5445-51.
29. Immink MM, Bekker MN, de Melker HE, Rots NY, Sanders EAM, van der Maas NAT. Study protocol of the PIMPI-project, a cohort study on acceptance, tolerability and immunogenicity of second trimester maternal pertussis immunization in relation to term and preterm infants. *BMC Infect Dis* 2021; **21**(1): 897.
30. Ajzen I. The theory of planned behavior. *Organizational Behavior and Human Decision Processes* 1991; **50**(2): 179-211.
31. Janz NK, Becker MH. The Health Belief Model: a decade later. *Health Educ Q* 1984; **11**(1): 1-47.
32. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2 ed; 1988.
33. Liaw A, Wiener M. Classification and Regression by randomForest: R news, 2002.
34. Anraad C, Lehmann BA, Visser O, et al. Social-psychological determinants of maternal pertussis vaccination acceptance during pregnancy among women in the Netherlands. *Vaccine* 2020; **38**(40): 6254-66.
35. Schwartz SH. Normative Influences on Altruism. *Advances in Experimental Social Psychology* 1977; **10**: 59.
36. Rivis A, Sheeran P, Armitage CJ. Expanding the Affective and Normative Components of the Theory of Planned Behavior: A Meta-Analysis of Anticipated Affect and Moral Norms. *Journal of Applied Social Psychology* 2009; **39**(12): 35.

CHAPTER 10

Maternal vaccination against pertussis as part of the National Immunization Program: a qualitative evaluation among obstetric care providers one year after the implementation in December 2019

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Abstract

Background

Immunization of pregnant women with a tetanus-diphtheria-and-acellular-pertussis (Tdap) vaccine is an effective and safe way to protect infants from pertussis before their primary vaccinations. Vaccine uptake among pregnant women is influenced by their care providers' attitudes toward maternal vaccination. This qualitative study aimed to evaluate the implementation of the maternal Tdap vaccination under the National Immunization Program of the Netherlands from the perspective of obstetric care providers.

Methods

In this qualitative and explorative study, we conducted in-depth interviews by telephone with obstetric care providers who were selected from a pool of respondents (convenience sampling) to a questionnaire in a previous study. The interviews were based on a semi-structured interview guide that covered three aspects of the implementation strategy: providers' overall experience with the implementation of maternal Tdap vaccination in the Netherlands; implementation logistics and counseling, and pregnant women referrals to municipal Youth Healthcare Centers. The interviews were recorded, pseudonymized and transcribed verbatim. Transcripts were analyzed according to the Thematic Analysis approach by two researchers independently in two phases of iterative coding, categorizing, reviewing and redefining until ultimately, emergent themes regarding maternal Tdap vaccination implementation were identified.

Results

Interviews with 11 midwives and 5 OB-GYN physicians yielded 5 major themes regarding the Tdap vaccination implementation strategy: challenges throughout the implementation process, views on maternal Tdap vaccination, general versus tailored counseling, provider responsibilities in vaccine promotion, and impact of materials for information delivery. Participants indicated that to improve provider attitudes toward Tdap vaccination, its implementation requires clear and transparent information about what is entailed, i.e., what is expected from obstetric care providers, how they can obtain information, and when their actions must be initiated. Participants demanded involvement throughout the implementation planning process. They preferred tailored communication with pregnant women over a generalized approach.

Conclusions

This study emphasized the importance of involving all relevant healthcare professionals in planning the implementation of maternal Tdap vaccination. Possible barriers perceived by these professionals should be taken into account in order to improve their attitudes toward vaccination, thus to increase uptake among pregnant women.

Background

Pertussis is a highly contagious respiratory disease, caused mainly by the bacterium *Bordetella pertussis*. Especially young unvaccinated infants (<6 months of age) are at risk of developing severe disease, resulting into hospitalization and sometimes death.[1,2] *B. pertussis* is known to circulate across all age groups in many countries, including the Netherlands, despite high children's vaccination coverage. Hence, the disease is readily transmitted by infected persons showing no typical clinical symptoms, as symptoms generally manifest milder and less typical in older children and adults, but these age groups may be a source of transmission to young infants.[3-6] A recent serosurveillance study estimated that yearly approximately 5.9% of all residents older than 7 years in the Netherlands was recently infected by *B. pertussis*, whether or not showing any disease symptoms.[7] Confirmed pertussis incidence rates in all age groups show epidemic peaks every 3 to 4 years, with infants under 5 months of age having the highest incidence ranging from 64 to 222 per 100,000 each year in the decade before the COVID-19 lockdown periods.[5,8]

Before receiving their primary vaccinations, infants depend on maternal antibodies for protection against infectious diseases. These antibodies are actively passed to infants during pregnancy through placental IgG antibody transfer.[9] Maternal vaccination against pertussis enhances the immunological protection that infants receive from their mother.[10,11] Therefore, the Dutch Health Council advised in 2015 that vaccination against tetanus, diphtheria and acellular pertussis (Tdap) should be offered to pregnant women in the Netherlands. Initially, women could obtain the vaccine at their own expense at their general practitioner, midwife or gynecologist, or municipal healthcare center. Vaccine uptake increased rapidly in 2018 and 2019, with vaccine coverages of approximately 13% and 26%, respectively.[12] Ultimately since December 2019, the vaccination has been included in the National Immunization Program (NIP) of the Netherlands, making it available to pregnant women free of charge.[13,14]

Vaccine implementation was coordinated by the National Institute for Public Health and the Environment (RIVM) in close collaboration with representatives from Dutch professional organizations for obstetricians, midwives, and youth public healthcare physicians and nurses.[14-19] The implementation included the development of guidelines for the maternal Tdap vaccination, describing tasks for all professionals involved in this maternal vaccination program and practical information. It was decided that obstetric care providers would make pregnant women aware of the maternal Tdap vaccination well before 22 weeks of gestation, and hand out an information packet that consists of a letter and a leaflet about

maternal Tdap immunization. Women would then be referred to Youth Healthcare Centers to receive the vaccination and more counseling if needed. The vaccination is offered from 22 weeks of gestation, i.e. the earliest opportunity for women get vaccinated. Nowadays, maternal vaccine coverage in the Netherlands ranges around 70%.[20,21]

Previous research has shown that the attitude of obstetric care providers toward maternal Tdap vaccination greatly affects its acceptance by pregnant women.[22,23] Although vaccination in general is broadly supported by the public, there is some hesitancy and opposition, especially to vaccination during pregnancy.[24,25] A well-organized implementation strategy provides a clear definition of responsibilities as well as practical tools and repeated training to enable obstetric care providers to facilitate information delivery to pregnant women.[26,27] This qualitative study aimed to evaluate the implementation of maternal Tdap vaccination in the Netherlands from the perspective of obstetric care providers, its planning, guidelines, and the first few months of availability through NIP, and investigate how the implementation reflected their attitudes toward maternal vaccination. In addition, we explored possible improvements for future implementations of vaccinations during pregnancy.

Material and methods

Study design

This qualitative and explorative study was performed according to a phenomenological approach in order to identify (novel) themes that may be specific for the unique Dutch situation for offering the maternal Tdap vaccination.

Selection of study participants

Obstetric care providers were selected from a pool of respondents to a prior questionnaire-study of maternal Tdap vaccination.[28] They were approached for the current study if they had indicated willingness to be contacted for further qualitative research. 852 midwives and 201 gynecologist or OB-GYN residents responded to the initial questionnaire that was sent to a nationwide group of obstetric care providers from all geographical areas within our country. Convenience sampling was performed within those who stated willingness to participate in further research (23% (n=194) and 15% (n=31), respectively). Among those, antenatal care providers were selected and invited for study participation, assuming that both disciplines would be included in our eventual study population. No further inclusion criteria or restrictions were imposed for participation, except for that the person had to provide obstetric care at the time of inclusion, which was

already mandated for completion of the questionnaire. Contact details for inviting study participants were stored in a safe environment separate from the database that was analyzed. Further details on procedures and results of the previous study were reported elsewhere.[28]

The study was performed in accordance with the Declaration of Helsinki. Medical ethical approval was not necessary as this study was considered 'non-interventional' by the Medical Research Ethics Committee of Utrecht under reference number 20-601/C.

Data collection

We conducted individual in-depth interviews by telephone, as the study was conducted during COVID-19 lockdown periods. The interviewer (NJ) was a female master student under guidance (by MI) of the Centre for Infectious Disease Control of the RIVM. Prior to conducting the interviews, there was no relationship between the interviewer and the participants. Pilot interviews were held with three (non-)obstetric care related healthcare professionals. Verbal informed consent had been obtained from all the participants before the start of each interview. The interviews were based on a semi-structured interview guide with open-ended questions (Table 1) regarding three aspects of Tdap implementation: 1) overall experience with the implementation of maternal Tdap vaccination in the Netherlands; 2) implementation logistics and counseling; and 3) pregnant woman referrals to Youth Healthcare Centers. It was developed based on the current knowledge of attitudes toward maternal vaccination among obstetric care providers and their effects on maternal vaccine uptake, and the results of the previous questionnaire study, unique for the Dutch Tdap vaccination implementation, and evaluated in consultation with several experts in the field of obstetrics, infectious diseases, and epidemiology.[22,28-36] The interview guide was evaluated after every four interviews. The interviews were recorded and transcribed verbatim and fieldnotes imbedded in transcripts. For confidentiality, we assigned study numbers to all transcripts, whereafter the transcripts were moved to a safe environment separately from the databases on the questionnaire. Only three researchers (NJ, MI and KvZ) had access to the transcripts, of whom only NJ was aware which persons had been included in the study. All transcripts have been individually discussed between the interviewer and one analyzer (MI).

Data analysis

MAXQDA qualitative analysis software version 20.0.7. was used for analysis of results. Transcripts were analyzed according to the Thematic Analysis

approach.[37,38] Two researchers (MI and KvZ) independently analyzed the transcripts in two phases to identify emergent themes systematically. The first phase of analysis consisted of coding of the transcripts, with MI coding all transcripts and KvZ coding six randomly selected transcripts. Before proceeding to the next phase, they discussed discrepancies in coded segments until consensus was reached. In the second phase, all coded segments were iteratively categorized by MI; and by KvZ for the same six she coded in the first phase. Potential themes were identified based on the categorized codes, then reviewed and redefined against the dataset to generate final themes that were relevant regarding the implementation. These are presented in the results section with verbatim quotations from the transcripts in Dutch that were translated to English by the researchers.

Throughout this study, we aimed to follow the trustworthiness criteria from Lincoln and Guba, i.e. credibility, transferability, dependability confirmability, to ensure the rigor of the results.[39] Only the transferability criterion could not be well-embedded in our study since basic demographics from the questionnaire data were unavailable.

Results

Interviews and themes

From March until May 2021, 16 interviews were conducted. Study participants consisted of 11 midwives, of whom 9 provided primary care (henceforth called primary care midwives) and 2 provided secondary care (secondary care midwives), and 5 physicians, of whom 4 were gynecologists (2 working in secondary care and 2 in tertiary care) and 1 was an OB-GYN resident. All participants agreed to be interviewed for this study following the initial invitation. The interviews lasted between 25-35 minutes, with one outlier of 10 minutes. After the fourth round of evaluating the interview guide - for which no substantive updates were necessary -, corresponding with interviews 13-16, we decided that data saturation had been reached.

Five major themes regarding the implementation emerged: 1) challenges throughout the implementation process; 2) views on maternal Tdap vaccination; 3) general versus tailored counseling; 4) provider responsibilities in vaccine promotion; and 5) impact of materials for information delivery. Table 1 indicates how the aspects of the interview guide related to the final themes. Corresponding categories, subcategories and example codes have been provided in Supplementary Table 1 for reproducibility of the study.

Table 1. Interview guide.

Aspect	Question
Overall experiences as to the implementation of maternal Tdap vaccination in the Netherlands	What is your general opinion about maternal Tdap vaccination?[2]
	How did you experience the implementation of the maternal Tdap vaccination?[1]
	How would you have led the implementation of the maternal Tdap vaccination, based on your current knowledge?[1,3]
	How could a future implementation of a maternal vaccination be improved?[1,3,4,5]
Implementation logistics and counseling	What does an average conversation about Tdap vaccination with a pregnant woman look like?[2,3,4,5]
	How do conversations about Tdap vaccination with pregnant women differ?[3,4,5]
	Does - and how does - the subject maternal Tdap vaccination return later throughout pregnancy?[3,4,5]
	What information materials do you use for informing pregnant women about the maternal Tdap vaccination?[5]
	What do you think of the information materials that you use for information delivery?[5]
Pregnant woman referrals to Youth Healthcare Centers	How would you describe your collaboration with Youth Healthcare Centers?[1,3,4]
	What is the added value of being notified by Youth Healthcare Centers that one of your clients/patients has received maternal Tdap vaccination?[1,4]
	How would you describe your role regarding the maternal Tdap vaccination?[3,4,5]
	How do you regard your role in relation to the role of Youth Healthcare Centers?[1,3,4,5]

Superscripted numbers indicate how the responses to questions from the interview guide predominantly related to the corresponding themes as presented in the results section: [1]challenges throughout the implementation process; [2]views on maternal Tdap vaccination; [3]general versus tailored counseling; [4]provider responsibilities in vaccine promotion; [5]impact of materials for information delivery.

1. Challenges throughout the implementation process

Participants generally agreed that the implementation required a concrete description of what Tdap vaccination as part of the NIP entails: what is expected from obstetric care providers, how they can obtain information, and when their actions must be initiated. The information they received about what actions to take during counseling, as well as training sessions and an e-learning that was made available, were highly appreciated by the participants, and increased their confidence when informing pregnant women about maternal Tdap vaccination.

Participants found it unfortunate that after the Health Council advised maternal Tdap vaccination, four years elapsed before it was available free under the NIP. In this interval, local initiatives arose to provide the vaccination to pregnant women at their own cost. The logistics that had been put in place for that process had to be reorganized after NIP included the maternal Tdap vaccination.

> *"Initially, we [midwives] worked together with general practitioners during the implementation [prior to inclusion within the NIP]. The GP would provide and inject it [the vaccine]. And actually, only a year later this was picked up by municipal healthcare services [Youth Healthcare Centers]." – interview 12, primary care midwife*

Once the vaccination was included under the NIP, participants needed a short period to get used to new procedures, after which execution became easier.

Some decisions made by policy makers were not fully supported nor well understood by all our participants. They argued that there were insufficient opportunities for providing input by healthcare providers during the planning process. Notably, many were unaware that representatives of their professional organizations had been involved throughout this process.

> *"It is very unclear to us [midwives] whether the KNOV [Royal Dutch Organization of Midwives], for example, was included in the meetings [for guideline development]. How did that go? What was the reason to ultimately decide for the Youth Healthcare Centers [to administer the vaccine]?" – interview 15, primary care midwife*

Several participants (predominantly primary care midwives) argued that vaccine uptake would have been higher if the whole process had been centralized and executed by the obstetric care provider. According to some, the current strategy of referring pregnant women to Youth Healthcare Centers for vaccination is an extra hurdle for the women.

> *"Pregnant women have to arrange it [obtaining the vaccine] themselves. They, themselves – especially if it concerns a first child – have to go to a new institution. This led to – well – that's a barrier after all. – interview 4, primary care midwife*

On the contrary, other participants (predominantly gynecologists) argued that

the guidelines could be easily maintained and were the reason for the (participant-reported) high vaccination coverage. Moreover, the implemented strategy provided advantages that would have been missed if both information delivery and vaccination had been centralized at obstetric care providers.

> *"The nurse who would usually initiate postpartum care now actually starts [informing about postpartum care] before that. So that they look at what kind of family it concerns, what could be possibly needed." – interview 8, gynecologist*

What was specifically being discussed during counseling by the professionals at Youth Healthcare Centers was unclear to many participants, regardless of the participants' awareness of any guidelines for counseling by their colleagues at these centers. However, they did not feel any urge to ask their regional Youth Healthcare facility for more information.

2. Views on maternal Tdap vaccination

Participants generally had a positive attitude toward maternal Tdap vaccination. Most of them believed themselves to be aware of the vaccine's purpose, its necessity, and its benefits as opposed to potential harms. After asking a secondary care midwife her opinion on maternal Tdap vaccination, she responded:

> *"It's about its [maternal Tdap vaccination's] efficiency. Its effectiveness has been proven and we have decided to start offering this vaccination, just like neighboring countries. That is why I am in favor of it being possible." – interview 9, secondary care midwife*

In addition to its safety and effectiveness, participants indicated that the reduced infant vaccination schedule was an important reason for pregnant women to accept Tdap vaccination. Infants of vaccinated mothers receive one fewer dose during their primary vaccination series and start the series one month later than infants of non-vaccinated mothers.

Although all gynecologists seemed in favor of maternal vaccination, some primary care midwives voiced doubts about immunization in general, including maternal Tdap vaccination. As maternal Tdap vaccination was often interpreted as a 'novel' vaccine, several participants were unaware of its established safety profile. A few said that vaccination during pregnancy seemed counter-intuitive:

> *"The feeling that you should decline many things during your pregnancy – such as certain foods, et cetera – but you would allow someone to inject yourself a vaccine. That feels odd and that is also why some pregnant women don't want this vaccination." – interview 3, primary care midwife*

Participants had the impression that from the perspective of pregnant women,

COVID-19 vaccination did not influence attitudes towards maternal vaccination or vaccine hesitancy. The uptake may have been reduced for a short while, since making an appointment for maternal vaccination during COVID-19 lockdown periods seemed difficult.

3. General versus tailored counseling

Most often, counseling by obstetric care providers consisted of a brief introduction to the vaccination and presentation of the NIP while handing over the information packet, perhaps accompanied by some arguments in favor of immunization. Only a few participants discussed arguments against vaccination. Pregnant women asked frequently what obtaining the vaccine entails and whether it is safe for their unborn child. Participants said they had to adjust their counseling to a woman's need for knowledge, in order to deliver the appropriate information according to her awareness of the vaccine:

> *"There is, of course, a group of women who already had it [Tdap vaccination] during [a previous] pregnancy, so you can get through that [counseling] a bit faster as they already consciously chose for it that time; and of course a group that has already heard or read about it, but did not receive it before; and a group that says they didn't notice anything about it at all." – interview 16, primary care midwife*

Participants felt the need to stay well-informed about maternal Tdap vaccination in order to improve their counseling. Being informed raised their confidence in counseling pregnant women, even to those who were reluctant to getting vaccinated. Some participants argued that the recommendations were "restricted to a generalized view" of pregnant women. More than the recommended time and effort was necessary for counseling pregnant women with a low socioeconomic status or a migration background.

> *"I find it very difficult to inform people in case of a language barrier. They are often vulnerable pregnant women. A huge amount of information transfer is lost there." – interview 9, secondary care midwife*

Time and effort was also necessary in the form of providing the vaccine at the hospital in case the pregnancy demanded medical attention, especially when longer-term hospital admission was required.

> *"I often see people who are admitted relatively early throughout pregnancy with [medical] issues. They tend to stay hospitalized for a long time. They are often unable to make an appointment [for Tdap vaccination] at the counseling center [Youth Healthcare Center]." – interview 6, gynecologist*

4. Provider responsibilities in vaccine promotion

The implementation guidelines suggest that obstetric care providers should merely introduce maternal Tdap vaccination in a superficial manner, and persuasive strategies for vaccine promotion are intentionally omitted from information for providers. However, many of our participants argued that informing pregnant women is their primary responsibility as the initial care provider. At the same time, while they can promote the vaccination, the choice whether or not to take the vaccine ultimately remains that of pregnant women.

> *"It is nowadays no longer the case that the doctor gives advice and that the pregnant woman blindly says 'Well that's a good idea, doctor, I'm going to do that.' It just doesn't work that way anymore. You have to eventually give patients the responsibility themselves." – interview 5, gynecologist*

Some participants indicated they counseled objectively, with no promotion of the vaccine, since they viewed their own opinion or attitude as irrelevant when it comes to the pregnant women's decisions about getting vaccinated.

> *"It's not about what I think or what I do. I think if you look at the information and odds of vaccine implications objectively, then it's easy to do it [getting vaccinated]. Though I can't – when I am counseling someone whether or not to take the vaccine – I can't tell them that I would take it." – interview 4, primary care midwife*

Some participants would rather merely mention the maternal Tdap vaccination while providing the information packet to pregnant women, and only perform the bare minimum of what is recommended in the guidelines, because no financial compensation is available for the time spent by obstetric care providers on counseling. A financial compensation may, according to some, contribute to the quality of vaccine promotion. Nevertheless, they felt compelled to invest in information delivery due to the relationship they had acquired with their clients or patients.

> *"I could also choose to only give the leaflet and say: "Go, find out what to do for yourself." But I don't think that is considered as providing sufficient care. It doesn't work like that either." – interview 15, primary care midwife*

5. Impact of materials for information delivery

Participants said that the information letter and leaflet were appreciated by their pregnant patients; the illustrations and patient-friendly layout of the leaflet seemed to positively affect vaccination intention. They concluded however, that pregnant women received an overwhelming amount of information materials in the first trimester of pregnancy, and that Tdap vaccination materials might best be

bundled with other materials to improve information delivery and information uptake by pregnant women. Participants also argued that handing over materials for vaccine promotion must always be supported by verbal information delivery.

> *"Most pregnant women take it [information packet] and then it ends up at the bottom of the pile." – interview 4, primary care midwife*

Participants mentioned occasionally that the information materials may be too difficult to understand by illiterate or non-Dutch-speaking pregnant women. The information materials were available in multiple languages, although hard copies were only available in Dutch. Therefore, the materials were less accessible, attractive and compelling to pregnant women with a migration background.

> *"If they don't speak the Dutch language, I will be forced to provide printed copies or send those to people by e-mail. It would be just useful if it's all in such a shining leaflet [like the leaflet written in Dutch], so to speak. That you can give it right away [physically]." – interview 9, secondary care midwife*

Discussion

This study indicated that the implementation of maternal Tdap vaccination in the Netherlands requires clear and transparent information about what the vaccination entails for obstetric care providers: what is expected from them, how they can obtain information, and when their actions must be initiated. Maternal Tdap vaccination was generally supported by obstetric care providers, mainly due to its proven effectiveness and its established safety profile. The participants were willing to invest time and effort in information delivery, even though the guidelines recommended only to make women aware of the vaccination, rather than counseling them extensively. As the pregnant women's initial care provider, participants felt constrained to provide sufficient obstetric care.

Some participants argued that obstetric care providers were "kept in the dark" regarding the decision that Youth Healthcare physicians should administer the vaccine, as opposed to the obstetric care provider. Although there was close collaboration with Dutch professional obstetric organizations throughout the implementation process, it seemed that many participants were unaware of the opportunity for providing input via their umbrella organizations. In future implementations, the inclusion of care providers should be emphasized by such organizations, as research shows that involving providers during guideline development reduces resistance to recommendations.[40,41] If professional organizations involve their members more actively, it may increase protocol adherence and improve attitudes toward vaccination among obstetric care

providers, leading ultimately to higher vaccine uptake among pregnant women.[23,26,42]

There was some contrasting between the different disciplines in obstetric care, predominantly between primary care midwives and gynecologists, with secondary care midwives in between. The debate on which party should facilitate vaccine administration, and whether or not this should be centralized, was a firm discussion between the disciplines that was already imbedded in the implementation. Even though it was occasionally interpreted as a 'loss' of the discussion as centralization was not realized, their attitude towards maternal vaccination seemed unaffected. Second, gynecologists had a generally more positive attitude towards maternal vaccination, compared to primary care midwives. This was in accordance with our previous questionnaire study.[28] Previous studies suggested that this is because gynecologists are better aware of the consequences, while among midwives, negative beliefs and concerns regarding vaccination, including vaccination in general, had risen.[43,44]

According to our participants, counseling of pregnant women about maternal Tdap vaccination cannot be standardized, as it highly depends on the women's individual needs for knowledge. Moreover, some pregnant women required a more extensive approach, e.g. in a first pregnancy or a complicated pregnancy requiring extensive medical support. Our study emphasized that tailored counseling is needed for the provision of appropriate advice, making women feel their concerns have been addressed so they feel comforted about maternal vaccination.[45-48] Illiterate or non-Dutch speaking pregnant women are, according to our participants, more difficult to reach in terms of vaccine-promotion. To our knowledge, only one study assessed the influence of health literacy on maternal vaccine acceptance with higher literacy associated with rejection of the vaccine.[49] Nevertheless, the authors excluded women impacted by illiteracy and language barriers, which prevented completion of the questionnaires. High literacy was, however, associated with higher COVID-19 vaccine acceptance.[50] According to our findings, the first step to better target these groups in the Dutch maternal Tdap vaccination program could be facilitated by creating hard-copy information materials in multiple languages including making available a linguistic simplified version and by providing information about specific logistics for vaccine delivery when pregnancies demand medical attention.

Several participants who basically supported Tdap vaccination in pregnant women were hesitant to promote it; they described their counseling approach as objective or irrelevant, since women would ultimately decide for themselves. However, research has shown the relevance of provider attitudes; both verbal and

non-verbal provider-patient communication greatly affect health-related outcomes, including vaccination intent among pregnant women.[51] Therefore, unwillingness to discuss or promote the vaccination could suggest to pregnant women that the provider has doubts about the vaccine. To improve care providers' attitudes, we recommend that future implementation strategies facilitate providers' needs and wishes, while also emphasizing that provider attitudes may subconsciously affect their counseling or its effect on pregnant women.

Our study has strengths and limitations. A strength of this study is that double coding was applied, thereby increasing the reliability of coding. As for the limitations, participants were selected from a pool of respondents to a prior questionnaire study, in which they indicated that they would like to participate in follow-up research. Therefore, only obstetric care providers who finished the questionnaire and provided their contact details could be included, possibly introducing selection bias.[52] Second, the interviews were conducted by researchers from the National Institute for Public Health, which is responsible for the implementation of the maternal Tdap vaccination. This link may have led some participants to speak less freely. On the other hand, some may have seen our evaluation as a unique opportunity to provide input for improvement of the implementation. In addition, the interviews were conducted by telephone due to the COVID-19 lockdown periods, which may have also contributed to hampered communication. Another limitation is that we asked participants for retrospective views on the implementation strategy and informational materials a full year after NIP included the vaccination; thus their recall may have been compromised. To reduce any other influence of recall bias, we started each interview by summarizing the different timepoints of the maternal Tdap implementation process and the date at which the vaccine was included within the NIP.

In conclusion, this study underlined the importance of involving the relevant healthcare professions, including individual care providers, during the implementation of a maternal Tdap vaccination in the NIP. Our participants generally supported the vaccination, but some were hesitant, especially about vaccination during pregnancy. Future implementation strategies involving antenatal care should focus on tailored information for pregnant women as opposed to generalized information that applies only to uncomplicated pregnancies.

Supplementary Table 1. The five major themes with corresponding categories, subcategories and example codes.

Theme	Category	Subcategory	Example code[a] (translated from Dutch)
1) Challenges throughout the implementation process	General process	Organization	*one must decide when the vaccination will be implemented*
		Training session(s)	*keep information provision this way*
		Naming the vaccine	*name 22-week-shot[b] follows up the 20 weeks anomaly scan quite well*
		Time lapse since advice	*inform care providers directly after advice of health council*
		Logistics pre-inclusion	*implementation was picked up together with GPs*
		Logistics post-inclusion	*messy start due to uncertainty on logistics*
		Execution	*execution became easier later on*
		Vaccine stock	*vaccines were not always available right after implementation*
	Allocation of roles	Current guidelines	*in doubt whether the vaccine is currently administered at the right place*
		Centralization	*the whole process needs to be put in one place*
	Collaborations	Contact with Youth Healthcare Centers	*contact is good, often concerns other things than maternal vaccination*
		Content of consult at Youth Healthcare Centers	*unaware how they [youth healthcare professionals] counsel*
		Post-partum care	*they initiate post-partum care during pregnancy*
		Availability	*contacting them takes some effort sometimes*

Supplementary Table 1. Continued.

Theme	Category	Subcategory	Example code[a] (translated from Dutch)
2) Views on maternal Tdap vaccination	Attitude towards maternal vaccination	Efficiency	*maternal pertussis vaccination has been proven to be efficient*
		Safety	*unavailable long-term effects of maternal vaccination*
		Necessity	*maternal pertussis vaccination prevents serious complications in their infant*
		Disease severity	*whooping cough may lead to death*
		Benefits of vaccination	*vaccination has a twofold strategy [prevention of disease and infant fewer vaccinations]*
		Drawbacks of vaccination	*odd feeling to have a vaccination injected during pregnancy*
		Vaccine components	*not okay that the vaccine is a cocktail [of vaccine components]*
	Attitude towards general vaccination	Infant vaccination	*that their baby may be vaccinated a month later is an incentive for women to accept the vaccination*
		Experiences with own children	*own children did not receive all vaccinations as well*
		COVID-19 vaccination	*during the corona time making an appointment [for maternal vaccination] was difficult for a while*

Supplementary Table 1. Continued.

Theme	Category	Subcategory	Example code[a] (translated from Dutch)
3) General versus tailored counseling	Consultation	Information provision and referral	*mentions the existence of the vaccination*
		Timing during pregnancy	*the intake [first appointment] is too early for [explaining] the maternal vaccination*
		Acceptance or rejection	*some women have principles against vaccination*
		Time and effort	*sometimes a challenge to discuss everything in addition to other things*
		Documentation in medical files	*women are asked whether or not they obtained the vaccination, which will be documented*
		Need for knowledge	*opinion on vaccinations differs between women*
	Pregnant women's situation	Primi- or multiparous women	*pregnant women compare the situation to their first pregnancy*
		Socio-economic status	*there are many socially vulnerable pregnant women*
		Hospitalization	*insufficient information [available] for hospitalized pregnant women*

Supplementary Table 1. Continued.

Theme	Category	Subcategory	Example code[a] (translated from Dutch)
4) Provider responsibilities in vaccine promotion	Job assignments	Self-perceived assignments	*my job is to educate women and to tell them the benefits comprehensively*
		Objective counseling	*the opinion of the care provider [on vaccination] does not matter*
		Persuasive approach	*care provider must deduct barriers and reduce thresholds*
		Ultimate decision	*give patients responsibility to decide themselves*
		Financial compensation	*all those extra tasks for midwives are not financially justified*
		Doubt whether or not to answer questions	*we [obstetric care providers] will be asked questions [instead of Youth Healthcare professionals]*
	Pregnant women's perspectives	Opinion on immunization (during pregnancy)	*different conversations with vaccine-critical women*
		Acquired relationship with care provider	*bond between midwife and pregnant forces midwife to counsel about maternal vaccination*

Supplementary Table 1. Continued.

Theme	Category	Subcategory	Example code[a] (translated from Dutch)
5) Impact of materials for information delivery	Mandated materials	Clarity – difficulty	*current materials for information are structured*
		Size and scope	*bundled materials should keep it manageable*
		Linguistics	*language barriers result into loss of information transfer*
		Literacy	*extra attention required for illiterate people*
	Self-composed additional materials	(Digital) mail, link to official website	*redirect women to the website for additional information*
		Other materials	*those thematic pink bandages are a good image for the vaccination*

[a] Example codes reflected solely the code, and not the marked segments from the transcripts. Quotations have been provided in the Results section of this article. [b] Official name for the maternal Tdap vaccination [in Dutch: 22-wekenprik]

References

1. Cherry JD. Pertussis in Young Infants Throughout the World. *Clin Infect Dis* 2016; **63**(suppl 4): S119-S22.
2. Kandeil W, Atanasov P, Avramioti D, Fu J, Demarteau N, Li X. The burden of pertussis in older adults: what is the role of vaccination? A systematic literature review. *Expert Rev Vaccines* 2019; **18**(5): 439-55.
3. de Greeff SC, Mooi FR, Westerhof A, et al. Pertussis disease burden in the household: how to protect young infants. *Clin Infect Dis* 2010; **50**(10): 1339-45.
4. Althouse BM, Scarpino SV. Asymptomatic transmission and the resurgence of Bordetella pertussis. *BMC Med* 2015; **13**: 146.
5. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. *Emerg Infect Dis* 2000; **6**(4): 348-57.
6. de Greeff SC, de Melker HE, van Gageldonk PG, et al. Seroprevalence of pertussis in The Netherlands: evidence for increased circulation of Bordetella pertussis. *PLoS One* 2010; **5**(12): e14183.
7. Versteegen P, Berbers GAM, Smits G, et al. More than 10 years after introduction of an acellular pertussis vaccine in infancy: a cross-sectional serosurvey of pertussis in the Netherlands. *Lancet Reg Health Eur* 2021; **10**: 100196.
8. van der Maas NA, Mooi FR, de Greeff SC, Berbers GA, Spaendonck MA, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? *Vaccine* 2013; **31**(41): 4541-7.
9. Ciobanu AM, Dumitru AE, Gica N, Botezatu R, Peltecu G, Panaitescu AM. Benefits and Risks of IgG Transplacental Transfer. *Diagnostics (Basel)* 2020; **10**(8).
10. Amirthalingam G, Campbell H, Ribeiro S, et al. sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. *CID* 2016.
11. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ* 2014; **349**: g4219.
12. Schurink-van 't Klooster TM, de Melker HE. The National Immunisation Programme in the Netherlands - Surveillance en Developments in 2019-2020, 2020.
13. Dossier vaccinatie tegen kinkhoest: doel en strategie. 2015. https://www.gezondheidsraad.nl/documenten/adviezen/2015/12/02/vaccinatie-kinkhoest-doel-en-strategie.
14. Kamp L, Isken L, Zonnenberg I, et al. Implementation strategy maternal pertussis vaccination: National Institute for Public Health and the Environment, 2018.
15. Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG). https://www.nvog.nl/.
16. Koninklijke Nederlandse Organisatie van Verloskundigen (KNOV). https://www.knov.nl/.
17. Jeugdartsen Nederland (AJN). https://ajnjeugdartsen.nl/.
18. Nederlands Centrum Gezondheid (NCJ). https://www.peristat.nl/.
19. Verpleegkundigen & Verzorgenden Nederland (V&VN). https://www.venvn.nl/.
20. Pluijmaekers AJM, de Melker HE. The National Immunisation Programme in the Netherlands: Surveillance and Developments in 2020-2021: National Institute for Public Health and the Environment, 2021.
21. van Lier EAGO, P.J.; Giesbers, H.; van Vliet, J.A.; Hament, J-A.; Drijfhout, I.H.; Zonnenberg-Hoff, I.F.; de Melker, H.E. Vaccination Coverage and Annual Report National Immunisation Programme Netherlands 2020 [in Dutch: Vaccinatiegraad en Jaarverslag Rijksvaccinatieprogramma Nederland 2020], 2021.
22. Anraad C, Lehmann BA, Visser O, et al. Social-psychological determinants of maternal pertussis vaccination acceptance during pregnancy among women in the Netherlands. *Vaccine* 2020; **38**(40): 6254-66.
23. Vishram B, Letley L, Jan Van Hoek A, et al. Vaccination in pregnancy: Attitudes of nurses, midwives and health visitors in England. *Hum Vaccin Immunother* 2018; **14**(1): 179-88.
24. Betsch C, Bohm R. Detrimental effects of introducing partial compulsory vaccination: experimental evidence. *Eur J Public Health* 2016; **26**(3): 378-81.
25. Paul KT, Eberl JM, Partheymuller J. Policy-Relevant Attitudes Toward COVID-19 Vaccination: Associations With Demography, Health Risk, and Social and Political Factors. *Front Public Health* 2021; **9**: 671896.

26. Vilca LM, Martinez C, Burballa M, Campins M. Maternal Care Providers' Barriers Regarding Influenza and Pertussis Vaccination During Pregnancy in Catalonia, Spain. *Matern Child Health J* 2018; **22**(7): 1016-24.
27. Chander S, Gonzalez-Casanova I, Chaves SS, et al. Antenatal care providers' attitudes and beliefs towards maternal vaccination in Kenya. *Gates Open Res* 2020; **4**: 19.
28. Immink MM, Pluijmaekers AJM, Bekker MN, de Melker HE, van der Maas NAT, van Zoonen K. Maternale vaccinatie tegen kinkhoest in het Rijksvaccinatieprogramma: evaluatie onder verloskundig zorgverleners 1 jaar na de implementatie in december 2019. *Infectieziekten Bulletin* 2022; **01**.
29. Varan AK, Esteves-Jaramillo A, Richardson V, Esparza-Aguilar M, Cervantes-Powell P, Omer SB. Intention to accept Bordetella pertussis booster vaccine during pregnancy in Mexico City. *Vaccine* 2014; **32**(7): 785-92.
30. Hill L, Burrell B, Walls T. Factors influencing women's decisions about having the pertussis-containing vaccine during pregnancy. *J Prim Health Care* 2018; **10**(1): 62-7.
31. Hayles EH, Cooper SC, Sinn J, Wood N, Leask J, Skinner SR. Pertussis vaccination coverage among Australian women prior to childbirth in the cocooning era: a two-hospital, cross-sectional survey, 2010 to 2013. *Aust N Z J Obstet Gynaecol* 2016; **56**(2): 185-91.
32. Ko HS, Jo YS, Kim YH, et al. Knowledge and Acceptability about Adult Pertussis Immunization in Korean Women of Childbearing Age. *Yonsei Med J* 2015; **56**(4): 1071-8.
33. Winslade CG, Heffernan CM, Atchison CJ. Experiences and perspectives of mothers of the pertussis vaccination programme in London. *Public Health* 2017; **146**: 10-4.
34. McQuaid F, Jones C, Stevens Z, et al. Factors influencing women's attitudes towards antenatal vaccines, group B Streptococcus and clinical trial participation in pregnancy: an online survey. *BMJ Open* 2016; **6**(4): e010790.
35. O'Shea A, Cleary B, McEntee E, et al. To vaccinate or not to vaccinate? Women's perception of vaccination in pregnancy: a qualitative study. *BJGP Open* 2018; **2**(2): bjgpopen18X101457.
36. Bodeker B, Walter D, Reiter S, Wichmann O. Cross-sectional study on factors associated with influenza vaccine uptake and pertussis vaccination status among pregnant women in Germany. *Vaccine* 2014; **32**(33): 4131-9.
37. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006; **3**: 77–101.
38. Nowell LSN, J.M.; White, D.E.; Moules, N.J. Thematic Analysis: Striving to Meet the Trustworthiness Criteria. *International Journal of Qualitative Methods* 2016; **16**: 1–13.
39. Lincoln YS, Guba EG. Naturalistic Inquiry; 1985.
40. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and Strategies in Guideline Implementation-A Scoping Review. *Healthcare (Basel)* 2016; **4**(3).
41. Wang Z, Bero L, Grundy Q. Understanding professional stakeholders' active resistance to guideline implementation: The case of Canadian breast screening guidelines. *Soc Sci Med* 2021; **269**: 113586.
42. Robbins SC, Leask J, Hayles EH, Sinn JK. Midwife attitudes: an important determinant of maternal postpartum pertussis booster vaccination. *Vaccine* 2011; **29**(34): 5591-4.
43. Maertens K, Braeckman T, Top G, Van Damme P, Leuridan E. Maternal pertussis and influenza immunization coverage and attitude of health care workers towards these recommendations in Flanders, Belgium. *Vaccine* 2016; **34**(47): 5785-91.
44. Dube E, Gagnon D, Kaminsky K, et al. Vaccination during pregnancy: Canadian maternity care providers' opinions and practices. *Hum Vaccin Immunother* 2020; **16**(11): 2789-99.
45. Frew PM, Randall LA, Malik F, et al. Clinician perspectives on strategies to improve patient maternal immunization acceptability in obstetrics and gynecology practice settings. *Hum Vaccin Immunother* 2018; **14**(7): 1548-57.
46. Gowda C, Dempsey AF. The rise (and fall?) of parental vaccine hesitancy. *Hum Vaccin Immunother* 2013; **9**(8): 1755-62.
47. Stockwell MS, Fiks AG. Utilizing health information technology to improve vaccine communication and coverage. *Hum Vaccin Immunother* 2013; **9**(8): 1802-11.
48. Quinn SC, Parmer J, Freimuth VS, Hilyard KM, Musa D, Kim KH. Exploring communication, trust in government, and vaccination intention later in the 2009 H1N1 pandemic: results of a national survey. *Biosecur Bioterror* 2013; **11**(2): 96-106.
49. Castro-Sanchez E, Vila-Candel R, Soriano-Vidal FJ, Navarro-Illana E, Diez-Domingo J. Influence of health literacy on acceptance of influenza and pertussis vaccinations: a cross-sectional study among Spanish pregnant women. *BMJ Open* 2018; **8**(7): e022132.

50. Siewchaisakul P, Sarakarn P, Nanthanangkul S, Longkul J, Boonchieng W, Wungrath J. Role of literacy, fear and hesitancy on acceptance of COVID-19 vaccine among village health volunteers in Thailand. *PLoS One* 2022; **17**(6): e0270023.
51. Moore SD, Wright KB, Bernard DR. Influences on health delivery system satisfaction: a partial test of the ecological model. *Health Commun* 2009; **24**(4): 285-94.
52. Grobbee DE, Hoes AW. Clinical Epidemiology: principles, methods, and applications for clinical research: Sudbury: Jones and Bartlett; 2008.

CHAPTER 11

Summary and general discussion

Summary

Introduction

In this thesis, several aspects of second-trimester maternal tetanus, diphtheria, and acellular pertussis (Tdap) vaccination between $20^{0/7}$-$24^{0/7}$ weeks (w) gestational age (GA) as opposed to later Tdap vaccination, i.e. $30^{0/7}$-$33^{0/7}$w GA are described. In addition to the interpretation of immunological findings, a public health perspective towards maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA was taken into account.

The results of a longitudinal cohort study entitled '**P**remature **I**nfants and **M**aternal **P**ertussis **I**mmunization' (PIMPI) are presented. This study addressed three major topics on maternal Tdap immunization strategies; 1) pertussis-specific antibody levels in term and preterm-born infants following maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA, compared with maternal Tdap vaccination between $30^{0/7}$-$33^{0/7}$w GA; 2) reactogenicity of maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA; and 3) pregnant women's acceptance towards maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA. The PIMPI-study focused specifically on the potential benefits of maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w in case of preterm birth, which was defined as birth before $35^{0/7}$w GA. The 35 weeks cut-off was chosen instead of a 37 weeks cut-off as in the international standard definition for preterm birth, since around 35 weeks GA, maternally-derived IgG antibody levels in the fetus are expected to exceed antibody concentrations in the blood of the mother. The study aimed to include a large group of premature infants born before 35 weeks GA and particularly before 32 weeks GA, since data in these groups are very scarce. Results from preterms following maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA were compared with those from term infants after maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA, and compared with data from a reference cohort of term infants born to mothers who were Tdap vaccinated between $30^{0/7}$-$33^{0/7}$w GA.

In the first part of this thesis, infant antibody levels against pertussis following maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA in both term and preterm infants are described. Furthermore; pertussis-specific antibody levels in mothers and infants following maternal Tdap vaccination in immunocompromised pregnant women, the reactogenicity and the safety of maternal Tdap vaccination in the second trimester of pregnancy are provided. Population background incidence rates of adverse pregnancy outcomes from before the Tdap vaccine-implementation in the Netherlands in 2019 are reported based on the Dutch Perinatal Registry. Furthermore, pertussis incidence rates in the Caribbean Netherlands based on a serosurveillance study from 2017 are reported. In the

second part of this thesis, other aspects of maternal immunization are addressed, like socio-psychological determinants that may underlie maternal Tdap vaccine-acceptance, and the antenatal care providers' point of view on maternal Tdap vaccination implementation, as part of the National Immunization Program.

Summary of chapters

Chapter 1 is the introduction of this thesis and describes pertussis and its clinical manifestation, the history and epidemiology of the disease, previous and current strategies for vaccination against pertussis including maternal Tdap vaccination. It also describes the current surveillance practices of the National Immunization Program in the Netherlands.

Part I

Chapter 2 describes the design of the PIMPI-study in full detail. The rationale for the study was provided with its objectives, its details on study procedures, inclusion criteria, sample size calculations and the applied statistical analyses.

Chapter 3 reports on maternal antibody levels in newborns following maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA. Results indicated that following maternal Tdap vaccination within this interval, term infants at the age of two months had twofold lower maternal-derived IgG antibody levels against pertussis toxin (PT) compared with vaccination between $30^{0/7}$-$33^{0/7}$w GA. This implies that maternal Tdap immunization before 24 weeks GA may be less effective and vaccination later in pregnancy may be preferred in order to achieve higher protective anti-pertussis antibody levels in term-born infants. After preterm birth, Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA resulted in similar (anti-PT) or slightly lower (anti-filamentous hemagglutinin and anti-pertactin) IgG antibody levels compared with term infants following maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA, but yet again levels were significantly lower than those in term-borns born to mothers vaccinated between $30^{0/7}$-$33^{0/7}$w GA. As no Correlate of Protection is defined, the clinical implications of lower maternal antibody levels in newborns after maternal Tdap vaccination before 24w GA in view of protection against severe clinical pertussis remain unknown.

Chapter 4 contains a brief report that describes the results of post-hoc analyses from the immunogenicity study described in Chapter 3. Although the study was not powered to evaluate early and later born preterm infants separately, data suggest that in particular the (very) early preterm infants (birth <$32^{0/7}$w GA) have lower *B. pertussis*-specific antibody levels at two months of age after maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA compared with term-borns

following maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA. Moderate-late-preterms (birth between $32^{0/7}$-$34^{6/7}$w GA) following maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA showed *B. pertussis*-specific antibody concentrations that were more in line with those from term infants (birth ≥$37^{0/7}$w GA). Nevertheless, term-borns following maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA still had around two-fold lower *B. pertussis*-specific antibody levels than after maternal Tdap vaccination between $30^{0/7}$-$33^{0/7}$w GA (chapter 3). Also, it seemed that antibody decay was significantly faster in early preterm infants (mean half-life for PT 21.7 days) compared with moderate-late preterms and term infants (mean half-lives for PT 32.9 vs 32.2 days, respectively). This difference was similar for the other Tdap-related antibody half-lives. Maternal-derived IgG antibody concentrations at birth need to be put into perspective by the differences in mean time intervals between maternal vaccination and delivery, which were in this study 6.3w for early preterms, 10.5w for late preterms, and 17.9w for term-born infants, all born to mothers Tdap vaccinated between $20^{0/7}$-$24^{0/7}$w GA. Antibody levels at birth and the quality of antibodies may also affect the decay rate in the first months of life. Lower levels at births and a faster decay rate will possibly offer even lower protection to very early preterm infants in the first moths of life. Since this is a post-hoc study with limited power due to low numbers of participants, these findings and potential implications merit further investigation.

Chapter 5 reports on a pilot study that investigated IgG antibody responses upon maternal Tdap vaccination in immunocompromised pregnant women treated for rheumatic disease. It was observed that maternal antibody levels are relatively unaffected by various immune-modulating drugs for rheumatic disease. However, cord blood sera from infants born to mothers treated with biologicals like Tumor Necrosis Factor alpha inhibitors (TNFis) showed significantly lower anti-PT IgG antibody levels after maternal Tdap vaccination compared with infants from mothers unexposed to TNFis or healthy mothers. According to literature, there is contracting evidence that TNFis may (mildly) reduce some vaccination responses and infants therefore may be less protected after single maternal Tdap vaccination in case the mother is exposed to TNFi. This may require early start with pertussis vaccination at 6 weeks of age in case of TNFi-exposure during pregnancy, as is currently advised within the Dutch National Immunization Program.

In **Chapter 6**, the reactogenicity of maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA was described. In general, symptoms within the first week after vaccination were mild and the majority of symptoms were transient within 1 to 5 days. 0.6% of vaccinated women reported fever (≥38.0 ˚C). We found no differences regarding vaccine reactogenicity between second and third trimester Tdap

vaccination. With respect to adverse events during pregnancy, around delivery and in newborns, data from our study with maternal Tdap vaccination between 20-24 weeks GA were compared with data on population level from 2018, i.e. before maternal Tdap vaccination was introduced in the National Immunization Program. No increased risks on adverse pregnancy outcomes were observed. Overall, second-trimester maternal Tdap vaccination, i.e. between $20^{0/7}$-$24^{0/7}$w GA, appears safe and well-tolerated by pregnant women and infants.

Chapter 7 addresses the background incidence rates of overall adverse pregnancy outcomes, unrelated to maternal Tdap vaccination. They were derived from the Dutch perinatal registry, that contain comprehensive data from over 98% of all pregnancies and deliveries in the Netherlands. These background data are required for putting into perspective any safety concerns that may rise when monitoring adverse pregnancy outcomes in the years following the implementation of the maternal Tdap vaccination in the Netherlands (as of December 2019). Based on the trends of several maternal and neonatal adverse pregnancy outcomes that were observed, no changes are expected in the years following maternal Tdap implementation, but regular adverse events and safety monitoring is in place.

Finally in **Chapter 8**, *B. pertussis* infection incidence is described over the Caribbean Netherlands (CN), based on a weighted serosurveillance study that was performed in 2017 on the islands that comprise the CN. Even though almost no cases of clinical pertussis were reported on the islands, it was estimated that based on serological anti-pertussis antibody measures, about 8% of all residents of 9 years and older in had been infected by *B. pertussis* during the past 12 months. The highest proportion of recently infected residents was observed in the age group of 12-29 years. Pertussis incidence remains severely underestimated by national disease surveillance systems which requires reporting of diagnostically confirmed cases of (clinical) pertussis infection, either in the Netherlands, CN and elsewhere. Most cases are not diagnosed, either because of mild or unrecognized clinical symptoms, or even in suspected cases, because diagnostics are not applied since there are no direct clinical consequences for treatment. In view of the high incidence of pertussis infections particularly in the child-bearing age group in the CN and as maternal Tdap vaccination has not yet been embedded in the National Immunization Program in the CN, there remains a great risk of transmission of *B. pertussis* to vulnerable (preterm) infants due to ongoing circulation of *B. pertussis* among the population. This means that maternal Tdap vaccination in the CN should be introduced together with close monitoring of the pertussis disease burden and vaccine effectiveness of maternal Tdap vaccination.

Part II

Chapter 9 reports on predictive and non-predictive socio-psychological factors regarding uptake of second trimester maternal Tdap vaccination, and shows that these factors do not differ from those of third trimester Tdap vaccination. The factors with the highest influence on maternal Tdap vaccine acceptance were intention and attitude towards taking the vaccine, beliefs on (long-term) safety and effectiveness, risk perception of (short-term) side effects of the vaccination and feeling moral responsibility to take the vaccine. Specifically for the Netherlands, women perceived the fact that the first vaccination of the baby can be delayed until three months of age instead of two months and one vaccination less is given (the 2+1 schedule instead of 3+1 schedule) after maternal Tdap vaccination, as beneficial. This means that healthcare providers should address these aspects when they discuss maternal Tdap vaccination with women early in pregnancy for an informed choice towards maternal Tdap vaccine acceptance.

According to the results of a study that was performed in preparation to the study of Chapter 10, and written in Dutch (**Appendix**), healthcare providers' attitudes towards maternal Tdap vaccination were generally positive once the maternal Tdap vaccination was implemented, though gynecologists were more in favor of maternal Tdap vaccination compared with midwives. The possible best way to enhance knowledge on maternal Tdap vaccination and pertussis in newborns is by facilitating (online) training before the implementation of maternal immunization strategies under the National Immunization Program and provide ongoing information on safety and effectiveness.

Chapter 10 also looked into healthcare providers' perceptions towards maternal Tdap vaccination, but in a qualitative manner. The interviews conducted with healthcare providers indicated that the implementation of a new vaccine in a new target group, and performed by a new group of professionals, requires clearness and transparency beforehand on what is expected. In case of maternal Tdap vaccination and antenatal care providers, clear and comprehensive information on the maternal Tdap vaccination strategy is demanded, and the actions required to take at different moments in time need to be put in place. This study emphasized the importance of involving the relevant healthcare professionals before and during the implementation of a new vaccination strategy. Possible barriers perceived by these professionals need to be taken into account in future maternal vaccine introductions in order to well-inform care providers on benefits and safety of maternal vaccination. This will ultimately help to increase uptake by pregnant women, since they rely often on the information and advice of their individual care providers.

The current summarizing **Chapter 11** is followed by the general discussion of this thesis, that reflects on the main findings related to the prevention of pertussis through maternal Tdap vaccination in early infancy, both in term and preterm infants. It also dives deeper into the aspects of maternal Tdap vaccine acceptance and (future) strategies for new maternal vaccinations targeting causative agents other than *B. pertussis*.

General discussion

Overview

Despite widespread vaccination, whooping cough caused by *Bordetella pertussis* (*B. pertussis*), remains a major cause of severe disease with high hospitalization rates and even fatal complications. Infections occur particularly during the first months of life before the newborn is protected by the primary series of pertussis vaccinations.[1-3] In older children and healthy adults, either following a previous infection or after a full series of vaccinations, the disease manifests milder and less typical, but reinfections occur frequently.[4,5] Therefore, older children and adults remain an important source of *B. pertussis* infections for newborns.[6,7] Maternal tetanus-diphtheria-and-acellular-pertussis (Tdap) booster vaccination protects newborns against pertussis in the first 2-to-3 months of life, as Tdap vaccination during pregnancy enhances the transfer of (*B. pertussis*-specific) IgG antibodies, and possibly also immune cells, from mother to child across the placenta.[8-14] Maternally-derived anti-pertussis toxin antibodies have been the focus of many maternal vaccination studies. The presence of high pertussis toxin IgG titers in the cord blood of newborns is correlated with a reduction in severe *B. pertussis* infections,[15] although the precise mechanisms of protection remain unclear. Many countries nowadays offer Tdap vaccination to pregnant women in the third trimester of pregnancy, as this is the stage in pregnancy at which transplacental antibody transfer is at its highest rate.[8] With third-trimester Tdap vaccination, this high transfer rate coincides with the peak in antibody concentration in the mother at around 2-4 weeks post Tdap vaccination, leading to a high level of maternal antibodies in the infant at birth.[2,16-18] Data on optimal timing of Tdap vaccination during pregnancy for maximal levels of maternal anti-pertussis toxin antibody concentrations in the infant, show however conflicting study results for term-born infants. Moreover, evidence on antibody levels and protection of preterm infants against pertussis and timing of vaccination during pregnancy remain scarce.[17-19] In case of premature delivery, Tdap vaccination after 30 weeks gestational age may often be too late, since sufficient transplacental antibody transfer to protect the baby against pertussis requires at least 2, but preferably at least 4 weeks, while an interval of 6-7.5 weeks was calculated for maximal maternal antibody levels at birth.[16] Preterm infants might therefore benefit from Tdap vaccination in the second, rather than the third trimester of pregnancy.[19] Nonetheless, robust data, particularly on maternal antibody transfer following immunization before 24 weeks gestational age, are lacking for both term and preterm infants.

Timing of maternal Tdap vaccination against pertussis regarding term-born infants

There is no consensus on the optimal moment during pregnancy to administer maternal Tdap vaccination for achieving protective maternal antibody levels in newborns at birth and a Correlate of Protection (CoP) is not available. Regarding term-born infants, several studies on the timing of maternal Tdap vaccination and maximal antibody levels at birth are however available.

- The recently published *OpTIMUM-trial* randomized pregnant women over three groups, with Tdap vaccination provided at ≤$23^{6/7}$w, between $24^{0/7}$-$27^{6/7}$w, and between $28^{0/7}$-$31^{6/7}$w gestational age (GA), respectively.[17] In total, 336 term-born infants were involved in this study. Pertussis vaccine-specific antibody concentrations, i.e. anti-pertussis toxin (anti-PT), anti-filamentous hemagglutinin (anti-FHA), and anti-pertactin (anti-Prn), in cord sera were equivalent over the three groups, according to the predefined study criteria, except that equivalence was not achieved for FHA. Both groups vaccinated earlier in pregnancy (before $28^{0/7}$w GA) showed significantly lower geometric mean anti-FHA antibody levels than those vaccinated later in pregnancy (between $28^{0/7}$-$31^{6/7}$w GA). For PT and Prn, the observed differences were smaller. Despite the fact that the predefined equivalence criteria were met, vaccination earlier in pregnancy showed lower antibody levels with a ratio of 0.76 for the group following Tdap vaccination before $24^{0/7}$w GA vs Tdap vaccination between $28^{0/7}$-$31^{6/7}$w GA.
- In another study, Gomme and colleagues combined five cohorts of mother-infant-pairs from multiple countries (n=475, all infants born at term), where mothers had received Tdap vaccination between 19-37w GA.[16] The authors from this multiple-country study concluded that the highest cord serum pertussis-specific antibody levels in term infants were acquired if the mother received a Tdap vaccination no later than at $32^{3/7}$w GA. As for the interval between vaccination and delivery, the authors observed stable high anti-PT levels in cord blood if mothers were vaccinated 6.5-20.5w prior to delivery.
- Healy and colleagues explored the effects of maternal Tdap vaccination between $27^{2/7}$-$36^{3/7}$w GA in term infants (n=312).[2] The results indicated that anti-PT levels in cord sera were highest after vaccination between 27 and 30w GA.
- Eberhardt and colleagues investigated Tdap vaccination in the second (between $13^{0/7}$-$25^{6/7}$w GA) versus the third trimester (between $26^{0/7}$-$41^{6/7}$w GA) regarding cord serum antibody levels against PT and FHA in term infants (n=335).[20] Interestingly, the authors' concluded that overall, second-trimester Tdap vaccination leads to significantly higher antibody levels against PT in cord

blood compared with third-trimester vaccination. However, further stratification into small groups according to GA at vaccination showed that cord blood antibody levels peaked if the mother was vaccinated around 30w GA.

There are no data on the impact of the stage of pregnancy on the immune response of maternal Tdap immunization, though one study reported on equal antibody responses to vaccination in pregnant compared with non-pregnant women.[21] In theory, differential hormonal status early or later in pregnancy might impact the vaccine response. As long as the precise mechanisms of protection against pertussis conferred to offspring by maternal Tdap vaccination is unknown and substantial knowledge gaps still exist, it is difficult to draw any firm conclusions on the optimal timing of Tdap vaccination in pregnancy. Also, the minimal level required for protection at both the humoral and cellular level, is unknown. Studies therefore often refer to the anti-PT antibody levels that appears to be associated with protection.[22]

This thesis focused on maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA and compared findings with maternal Tdap vaccination later in pregnancy at $30^{0/7}$-$33^{0/7}$w GA.[23] The conclusions of the studies are in line with the optimal timing of maternal Tdap vaccination in the first period of the third trimester, as Tdap vaccination between $30^{0/7}$-$33^{0/7}$w GA was found to be superior to $20^{0/7}$-$24^{0/7}$w GA, with twofold higher antibody levels against PT in cord sera of term-born infants and at the age of two months. In the multiple-country study from Gomme and colleagues, mathematical models suggest that an interval of at least 7.5 weeks between maternal Tdap vaccination and delivery is required to achieve the highest cord blood antibody levels in both term and preterm infants.[16] The findings presented in this thesis suggest however that maternal Tdap vaccination before 24w GA leads to significantly lower anti-PT antibody levels in term-borns as compared to maternal Tdap vaccination between $30^{0/7}$-$33^{0/7}$w GA and even lower levels in preterms. The finding that $20^{0/7}$-$24^{0/7}$w GA Tdap vaccination leads to significantly lower antibody levels in cord blood compared with vaccination between $30^{0/7}$-$33^{0/7}$w GA may possibly and at least partly be explained by the fact that the peak of antibody levels in the mother 2-4 weeks following maternal Tdap vaccination, does not coincide with optimal antibody transfer over the placenta that occurs in the third trimester.[17] In case of early maternal Tdap vaccination, i.e. before 24w GA, the antibody levels in the mother would have already declined in the third trimester. A longer time period for antibody transfer time may compensate the lower efficacy of antibody transfer in the second trimester. Together, for optimal antibody levels in term infants, maternal Tdap vaccination in

the early third trimester appears optimal for infants born at term.

Timing of maternal vaccination against pertussis regarding premature infants

Despite the availability of several studies in term infants, evidence on optimal timing of maternal Tdap vaccination regarding preterm infants remains scarce.

- A follow-up study from Eberhardt and colleagues investigated Tdap vaccination in the second trimester (between $13^{0/7}$-$25^{6/7}$w GA) versus the third trimester (between $26^{0/7}$-$41^{6/7}$w GA) regarding cord serum antibody levels against PT and FHA in preterm infants.[19] In total, 85 premature infants were included, but only 17 were born <$34^{0/7}$w GA and none <$30^{0/7}$w GA. Comparison between two small subgroups of these 17 preterms born between $30^{0/7}$-$33^{6/7}$w GA, with 8 mothers vaccinated in the second trimester vs 9 mothers in the third trimester, resulted in higher geometric mean concentrations (GMC) of anti-PT IgG in cord blood from infants after second-trimester Tdap vaccination. This suggests that that in case of preterm labour between $30^{0/7}$-$33^{6/7}$w GA, maternal Tdap vaccination in the second trimester is beneficial, but sample sizes were too small to draw firm conclusions.
- The aforementioned *OpTIMUM-trial* was unable to draw any conclusion on optimal timing of maternal Tdap vaccination in case of preterm birth, due to a small number of preterm-born infants included in the study, with 4 preterm mother-infant-pairs in each of the three groups (mothers were Tdap vaccinated at a 1:1:1-ratio at ≤$23^{6/7}$w, between $24^{0/7}$-$27^{6/7}$w, or between $28^{0/7}$-$31^{6/7}$w GA) and a median GA at birth of $33^{5/7}$w, $33^{2/7}$w, and $35^{6/7}$w GA, respectively.[17]
- Maertens and colleagues were the first to perform analyses on preterm infants from Tdap vaccinated mothers with a larger sample size, i.e. 82 preterms born with a mean GA of 30.9w at delivery.[18] However in this study, the time window for maternal Tdap vaccination ranged between $24^{0/7}$-$32^{0/7}$w GA. The authors concluded that there was no beneficial effect of earlier maternal Tdap vaccination on a continuous scale within the 24-32w GA range regarding antibody levels against PT at birth in preterms. However, an enlarged time interval between maternal Tdap vaccination and delivery was associated with significantly higher antibody levels against PT in cord blood in preterm infants.

Altogether, the question whether or not preterms benefit from maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA rather than in early third-trimester remains therefore largely unanswered and may also vary between early and late preterms, e.g. birth <$32^{0/7}$w GA vs ≥$32^{0/7}$w GA, respectively. The findings presented in this

thesis add to the current knowledge that maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA may lead to almost similar antibody levels between term and preterm-born infants. However, for more context of timing of vaccination regarding preterms, much larger follow-up studies that assess pertussis-specific antibody transfer in case of early and later preterm birth are required to investigate potential differences in antibody levels at birth following maternal Tdap vaccination at $20^{0/7}$-$23^{6/7}$w, $24^{0/7}$-$26^{6/7}$w, $27^{0/7}$-$29^{6/7}$w or $30^{0/7}$-$33^{0/7}$w GA.

The association between timing of maternal Tdap immunization and effectiveness of protection against pertussis in infancy

The clinical implications of the lower antibody levels in infants born to mothers who are Tdap vaccinated before 24w GA are unknown. Thus far, no CoP against clinical pertussis is available. This means that while the presence of high anti-PT IgG concentrations in the cord blood of newborns is correlated with a reduction in severe pertussis infections,[24] a minimal level of maternal antibodies against pertussis in cord blood required for protection against clinical severe disease is unknown. Moreover, no studies are available that link data on efficacy and effectiveness of maternal Tdap vaccination to maternally-derived anti-PT levels in cord blood or at two months of age. In addition, higher IgG anti-pertussis antibody levels in cord blood may not be the only explanation why newborns are better protected against pertussis. It was demonstrated that after maternal Tdap vaccination, pertussis-specific IgA and to a lesser extent IgG and IgM are also passed to newborns through breastmilk, allowing for a continued transfer of maternal antibodies and protection.[25,26] Quantitative maternal antibodies alone may not explain the l protection provided by maternal Tdap vaccination. In addition to height or subclass of anti-PT-antibody levels, also antibody avidity may contribute to protection against pertussis. Cellular immunity may play a pivotal role.[24,27]

Epidemiological data from Public Health England showed that in 2016 – after four years of maternal Tdap vaccination recommendation at ≥28w GA – maternal Tdap vaccine effectiveness (VE) was about 90% (95% confidence interval (CI) 86-93) up till two months of age, and 91% (95% CI 86-93) until three months of age.[11] After widening this time window for maternal Tdap vaccination from ≥28 weeks GA to ≥16 weeks GA from April 2016 onwards, it was recently estimated that the VE up till two and three months postnatal age had remained high, i.e. at 88% (95% CI 85-91) and 89% (95% CI 86-91), respectively, in case there was a time interval between maternal Tdap vaccination and delivery of at least two weeks. Maternal vaccine coverage within ≥13 weeks prior to birth increased from 5% to approximately 40%

since this intervention. These VE-estimations were based on a population-based sample of 108,455 live births and pertussis hospitalizations, including an unknown number of preterm infants. Unfortunately, VE data stratified for gestational age could not be made available. Therefore, these VE percentages remain overall estimations.[28] The fact that the VE did not change significantly following the shift of the time window for vaccination cannot be directly related to efficacy of maternal Tdap vaccination and IgG levels against pertussis in infants after early (before $24^{0/7}$w GA) versus later maternal Tdap vaccination. The study did not present individual data on gestational age at delivery and timing of maternal Tdap, and other data, e.g. on breastfeeding. Another issue to be taken into account, is that it was recently reported that the type of anti-pertussis vaccination series the mother received during infancy – whole cell pertussis (wP) vaccine or acellular pertussis (aP) vaccine – induces different antibody levels upon maternal Tdap vaccination and hence impacts antibody transfer during pregnancy.[29] The majority of women who were included in the PIMPI-study were most likely primed with a wP vaccine in infancy, because aP vaccination in the infant primary vaccination series was introduced in the Dutch National Immunization Program (NIP) only from 2005 onwards. The upcoming generation of women of childbearing age are vaccinated after 2005, and therefore primed with aP vaccines. These are factors that future studies should look into.

Many studies have reported on the contribution of non-PT anti-pertussis IgG levels for protection against clinical pertussis and the relevance of T-cell immunity, but particularly in older children and adults.[30] Rather than solely IgG antibodies, maternal Tdap vaccination may protect the newborn potentially also by transfer of cellular immunity.[8,31] Maternal vaccinations have been shown to influence maternal microchimerism in infants, e.g. a recent study demonstrated increased $CD4^+$-T cell responses following maternal bacillus Calmette-Guérin (BCG) vaccination.[32]

In summary; although anti-PT antibody levels are associated with protection against disease, there remains the need of better understanding the CoP mechanisms against *B. pertussis* and clinical pertussis symptoms. This would substantially contribute to new pertussis vaccine development, with the aim to prevent both clinical disease and transmission of *B. pertussis*. Only then, anti-pertussis vaccination strategies can be improved and induce herd protection without the need of repeated maternal vaccination.

Implications for infant primary vaccination series

Before the introduction of maternal Tdap vaccination in the Netherlands, all

infants were eligible for a DTaP-IPV-Hib-HepB vaccination schedule at 2, 3, 4 and 11 months of age. After introduction of maternal Tdap vaccination, it is recommended that all newborns of timely Tdap vaccinated mothers receive a DTaP-IPV-Hib-HepB vaccine at three, five and eleven months of age. The reason for the delay was that timely maternal Tdap vaccination lead to higher anti-PT antibody concentrations in term infants until three months of age compared to term infants at two months of age when the mother was unvaccinated. At the same time, this delayed first dose reduces the influence of blunting of the vaccine response upon the NIP vaccinations.[23,33-35] An extra vaccine at the age of two months (i.e. an adapted schedule) after maternal Tdap vaccination is advised if; the infant is born after a pregnancy duration shorter than 37 weeks; the interval between vaccination and delivery is shorter than two weeks; the mother is carrier of hepatitis B; or the mother is immunocompromised as a result of underlying disease and/or treatment with disease-modifying antirheumatic drugs. Infants from unvaccinated mothers also receive this additional dose at two months.[36] Many countries have enrolled different strategies for timing of the first infant primary vaccination against pertussis. According to the European Centre for Disease Prevention and Control (ECDC), nineteen European countries recommend starting the primary vaccine series against pertussis at two months of age, both in term and preterm infants. Nine of these nineteen countries recommend Tdap vaccination for all pregnant women.[37,38] Ten other European countries recommend starting at three months of age, but these countries have all enrolled a maternal Tdap vaccination strategy (although Norway only advises maternal Tdap vaccination during epidemics).[37,38]

The PIMPI-study was performed in order to evaluate the current Dutch advice for maternal Tdap vaccination from 22 weeks GA age onwards. A longer interval between vaccination and delivery might improve antibody transfer in term infants but it may in particular be beneficial for preterms. It was anticipated that early vaccination would allow to skip the extra pertussis vaccination in the adapted schedule at 6-9 weeks of age for a probable moderate-late-preterm infant group (birth ≥32 weeks GA). It was also demonstrated in a post-hoc analysis that moderate-late-preterm infants, who comprise 84% of all preterms born in the Netherlands,[39] had similar anti-PT levels as term infants. Moderate-late-preterms seem to benefit from similar IgG antibody levels against PT compared to term-born infants in case of vaccination before $24^{0/7}$w GA. However, since the anti-PT antibody levels after maternal Tdap vaccination before 24 weeks GA were at least a twofold lower compared with Tdap vaccination between $30^{0/7}$-$33^{0/7}$w GA, it is not clear whether preterms will be sufficiently protected, despite the fact that moderate-late preterms have the same anti-PT levels as terms after early maternal

Tdap between $20^{0/7}$-$24^{0/7}$w GA. Since preterms have a higher risk for hospitalization in case of pertussis, as a matter of precaution, we would now advise to uphold the current extra DTaP-IPV-Hib-HepB vaccination for preterms with the schedule starting at 6-9 weeks (3+1 schedule), even if the mother was Tdap vaccinated during pregnancy. As described above, quantitative anti-PT antibody data alone do not tell the full story as antibody functionality and cellular immunity may also be crucial and studies investigating this are primarily required before changing the current vaccination strategy for preterms in the future.

Examples of other knowledge gaps regarding maternal immunization against pertussis

Up till now, most studies on maternal Tdap vaccination concern healthy women and healthy term born infants. However, there are also subgroups of pregnant women or children that need special attention.

A growing number of women with rheumatic disease, inflammatory bowel disease or other immune-mediated conditions, is treated with immunomodulating drugs, also during pregnancy. In case a pregnant woman is immunocompromised, either based on the underlying disease or by treatment with disease-modifying antirheumatic drugs or both, this may impact the response upon maternal Tdap vaccination and hence antibody transfer to the fetus. A pilot study included in this thesis indicates that, although most Disease-Modifying Anti-Rheumatic Drugs (DMARDs) do not interfere with maternal Tdap vaccination responses in the mother, tumor necrosis factor alpha inhibitors (TNFis) may lead to lower pertussis-specific antibody levels in cord serum. This supports the current approach in the Netherlands to advice early vaccination against pertussis according to the the adapted 3+1 schedule starting at 6-9 weeks of age, in case there was TNFi-treatment during pregnancy.

To enhance anti-pertussis antibody levels during pregnancy after maternal vaccination, a second booster dose during pregnancy might be considered. Repeated Tdap vaccination booster doses within weeks-or-months in healthy males and non-pregnant females are currently not recommended, although it is supposed to result in slower waning of antibodies, and no safety concerns have risen.[40] Whether this method may be appropriate for pregnant women in order to provide better protection for infants shortly after birth should be evaluated based on future research investigating this topic. These studies should mainly focus on the balance between safety and benefits of repeated booster doses during a single pregnancy, with respect to vaccine acceptance and also to the perspective of upcoming other non-pertussis maternal vaccinations.

Another potential risk group, apart from premature-born infants, are infants born after a fetal growth restriction (FGR) during pregnancy. Nowadays in the Netherlands, youth healthcare physicians may decide to apply the adapted vaccine schedule (starting from two months of age) to FGR-infants. Often, FGR-infants are a subgroup of small for gestational age (SGA) neonates and/or preterm infants, but sometimes fetal growth restriction also occurs in infants with a normal birth weight and term pregnancy duration. SGA is defined as a birth weight ≥2.0 standard deviations under their mean birth weight, adjusted for GA. The majority of SGA-infants are constitutionally small with no increased risk of long-term morbidity and mortality. In contrast, FGR-infants do suffer from long-term increased risk of morbidity and mortality. The most common cause of FGR is a placental dysfunction leading to insufficient transfer of oxygen and nutrients.[41] It may be plausible that also the transfer of maternal antibodies and/or immune cells is hampered in FGR-infants. Currently however, no evidence of a decreased transplacental transfer rate to FGR-infants upon maternal Tdap vaccination is available. Now that the number of studies on maternal Tdap vaccination in combination with prematurity is growing, future research that investigates maternal Tdap vaccination targeting this specific FGR-infant group is urgently needed.

Second- or third-trimester maternal Tdap vaccine acceptance

According to the study on maternal Tdap vaccine acceptance between $20^{0/7}$-$24^{0/7}$w GA by pregnant women as presented in Chapter 9 in this thesis, it was found that factors that influence maternal Tdap vaccine acceptance appear to be similar in the second and third trimester. A limitation of the study was that it was performed in a population with proportionally high maternal Tdap vaccine uptake (about 95% in the second trimester), which implies that this is not necessarily a representative population. However, the study findings suggest that women are willing to obtain the vaccine early in pregnancy, which offers a broader window of time during pregnancy to get vaccinated. A recent study reported that women prefer to be informed far ahead of getting the maternal vaccine, preferably already early in pregnancy, i.e. well before 20 weeks GA.[42] Healthcare professionals are encouraged to inform women early in pregnancy in order to facilitate the informed-choice towards vaccine acceptance and possibly increase vaccine uptake. Also, for public health reasons, countries may offer maternal Tdap vaccination at a wider time-window of vaccine eligibility. In England, the larger opportunity to get maternal Tdap vaccination as a result of the wider time window for vaccination during pregnancy, from 16 weeks GA onwards since 2016 instead of 28 weeks, appeared to have increased maternal Tdap vaccine uptake.[28] The authors of this

study concluded that since 2016, vaccine coverage increased (from ±60% to ±75%) with approximately 40% of pregnant women who had received maternal Tdap vaccination ≥13 weeks prior to birth, whereas this was less than 5% before widening the interval. The knowledge that pregnant women seem to be willing to accept maternal Tdap vaccination early in pregnancy is particularly relevant when the vaccination may be implemented earlier in pregnancy, if future research might point to the benefits of early vaccination.

Targeting other vaccine-preventable diseases through maternal immunization

Since the implementation of maternal Tdap vaccination under the NIP in the Netherlands, in December 2019, the national vaccination coverage fluctuates around 70%.[43] This is currently 69% in England,[44] while in Flanders, the northern region of Belgium, it was recently reported that maternal Tdap vaccination coverage ranged around 85%.[45] In many countries, next to maternal Tdap vaccination, maternal influenza vaccination is routinely advised for all pregnant women, in order to protect women during pregnancy against influenza and the infant both before and after birth. Normally, an average influenza season of 2.5 months yields 25 hospital admissions in every 10,000 women at the end of pregnancy due to an influenza-related complication.[35] In addition, the hospitalization rate for influenza or complications is highest among the youngest of infants. Maternal influenza vaccination offers protection while there are no licensed influenza vaccines for infants younger than 6 months of age.[46] Still, maternal influenza vaccination uptake tends to be much lower than Tdap vaccination in many countries, e.g. 62% in Flanders and 25% in England.[45,47] According to a recent study, a reason for a higher uptake of maternal Tdap vaccination than influenza vaccination during pregnancy was because mothers were generally more aware that maternal Tdap vaccination protects their infant, while they believed maternal influenza vaccination would benefit themselves rather than their baby.[48] They were generally unaware of any infant hospitalization risk due to influenza. In September 2021, the Dutch Health Council recommended to extend the invitation for seasonal influenza vaccination to more risk groups, including all pregnant women without underlying disease.[49] Pregnant women with risk factors for severe influenza disease or influenza-related complications were already invited for the flu vaccination.[50] Timing of maternal influenza vaccination in pregnancy is an issue that differs from timing of maternal Tdap vaccination. The reason for vaccination from 22 weeks GA onwards is to protect both mothers in the last trimester and infants in the first months of life, rather than the protection of

solely the mother during pregnancy. Vaccination before 22 weeks GA may also protect the infant due to maternal IgG antibody transfer, but influenza vaccination during the first trimester or early second trimester for risk groups primarily aims to protect women against disease during pregnancy. In line with the results on Tdap vaccination acceptance in chapter 9 of this thesis, a recent study from the Netherlands showed that the main reasons for pregnant women to get vaccinated against influenza, was to protect their infant against infection (71%), followed by preventing serious illness for the infant (54%).[51] Complementary to our findings was that vaccination intent seemed to increase with gestational age. For now, healthcare professionals are encouraged to create awareness around the opportunity to receive maternal influenza vaccination. Like with maternal Tdap vaccination, the implementation of maternal influenza vaccination as part of the Dutch NIP shall be evaluated in the near future.

The health council recently published a new recommendation for an immunization strategy against respiratory syncytial virus (RSV). A first RSV-infection can be very dangerous for infants under six months of age, particularly if premature and in other risk groups. However, a vaccine for infants is yet unavailable. It was recently estimated that globally, infants younger than six months suffered from 6.6 million RSV-associated acute lower respiratory infection episodes, 1.4 million hospital admissions due to RSV infection, and 13,300 RSV-associated in-hospital deaths.[52] In the Netherlands, an incidence of RSV-associated hospitalization of 1.8% was estimated in the first year of life of term-borns, with the highest disease burden among those younger than three months.[53] Recently, a maternal prefusion F protein-based RSV-vaccine has been approved by the US Food and Drug Administration and European Medicines Association.[54,55] Current preferred product characteristics for maternal RSV vaccination have VE estimates of 70%, with infant protection against clinical disease to at least 4 months after birth, according to the WHO.[56] Another strategy for the prevention of RSV-mediated acute lower respiratory infection in very young infants is the administration of the recently registered monoclonal antibodies with an extended half-life, e.g. Nirsevimab.[57,58] The Dutch health council has recently advised to start with monoclonal antibody injections for newborns to protect against RSV.[59] To date, infants with specific underlying risk factors already receive monthly monoclonal antibodies in their first RSV risk period to prevent severe disease.[60,61]

Until recently, COVID-19 vaccination was advised during pregnancy in the Netherlands. During potential future outbreaks, maternal COVID-19 vaccination may become available again in order to prevent disease in the mother prior to the delivery and to prevent possible pregnancy complications like premature birth.

Offering maternal COVID-19 vaccination in the future may be reconsidered in the future, depending of the protection offered by the vaccine against upcoming COVID-19 variants, safety and e.g. the burden of disease in pregnant women. Apart from these vaccines, also other vaccines for maternal immunization are in preparation, e.g. cytomegalovirus or Streptococcus group B.

Based on the abovementioned possible (upcoming) maternal immunization strategies, the prevention of vaccine-preventable diseases in infants before infant primary vaccinations would depend on multiple different vaccines given during pregnancy as long as no specific vaccines for the general population are available that offer sufficient herd protection for pregnant women and infants in the first months of life. Multiple vaccinations during a single pregnancy for infant protection would most certainly impact the vaccine acceptance by pregnant women against certain diseases, as demonstrated by the aforementioned differences in vaccine uptake between maternal pertussis and influenza vaccination. Combining vaccines against different agents may be a possible solution, but timing of maternal vaccination for protection of the mother and infant may differ between vaccines. Also, possible interference of maternal vaccination with development of immunity in the infant requires more research, e.g. in the field of cellular immunity.

Challenges in monitoring the pertussis disease and vaccine surveillance

Monitoring the effectiveness of maternal pertussis vaccination based on whooping cough incidence in the Dutch national population may come with major limitations. For instance, the first COVID-19 lockdowns were announced (February 2020) a few months after maternal Tdap vaccination had been embedded within the NIP in the Netherlands (December 2019). A short-term consequence of the pandemic with physical distancing and other non-pharmaceutical measures, was a decrease in the incidence of multiple vaccine-preventable disease and notifications. This was most outspoken for respiratory infections, with a 75-97% reduction for overall respiratory infections and a 77% reduction for pertussis infections, according to the reported number of cases.[62] These incidence rates of pertussis hamper the availability of sufficient data to assess vaccine effectiveness estimates and the impact of the maternal Tdap vaccination strategy.

Evaluation of (maternal) vaccination strategies depends on the availability of data on vaccination coverage and timing, clinical characteristics of the women and infants, and detailed information of disease cases. In the Netherlands, unfortunately the documentation of an administered maternal vaccine is registered in a maternal registry, while characteristics like gestational age, birth weight, or pertussis-related illness are registered in another registry specifically for neonates

and children. These data are kept separated for privacy reasons. This complicates estimates on the coverage and vaccine effectiveness of maternal Tdap vaccination, and hamper the evaluation of the reduced 2+1 DTaP-IPV-Hib-HepB vaccination schedule, starting at three months of age. Population-wide VE studies, stratified for gestational age at vaccination and birth, in the Netherlands, like the aforementioned study from Amirthalingam and colleagues from England, may therefore be difficult to perform under the current circumstances.[28]

Conclusion

This thesis investigated several aspects of second-trimester versus third-trimester maternal tetanus, diphtheria, and acellular pertussis vaccination. Immunization before 24 weeks gestational age appears suboptimal for transplacental antibody transfer and thus may weaken protection against pertussis in term-born infants. Tdap vaccination before 24 weeks gestational age showed however similar anti-PT antibody levels in preterms born after 32 weeks GA compared with term-borns after Tdap vaccination between 20-24 weeks of gestation, but it is unknown whether the lower antibody levels offer sufficient protection to (late) preterms or even in term-borns. As long as no Correlates of Protection are available, it is difficult to determine the optimal timing for vaccination for term-borns, but in particular for preterms. Also, the half-life of antibodies as well as the antibody quality (functions like avidity) are important. Cellular immunity after maternal immunization is another relevant field. With many more upcoming maternal vaccinations in the near future, and the uncertainty what this will do with maternal vaccine acceptance, it remains important to closely monitor vaccine coverage and effectiveness shortly after implementation. Addressing these and other knowledge gaps is required for development of optimal maternal vaccination strategies. This is particularly urgent, since in the winter of 2023-2024 in the Netherlands a new surge in pertussis has started and pertussis will remain endemic until better vaccines are developed and optimal vaccine coverage has been achieved.

References

1. Kandeil W, van den Ende C, Bunge EM, Jenkins VA, Ceregido MA, Guignard A. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. *Expert Rev Vaccines* 2020; **19**(7): 621-38.
2. Healy CM, Rench MA, Swaim LS, et al. Association Between Third-Trimester Tdap Immunization and Neonatal Pertussis Antibody Concentration. *JAMA* 2018; **320**(14): 1464-70.
3. WHO pertussis. 2022. https://www.who.int/health-topics/pertussis.
4. Edwards K, Freeman DM. Adolescent and adult pertussis: disease burden and prevention. *Curr Opin Pediatr* 2006; **18**(1): 77-80.
5. Rothstein E, Edwards K. Health burden of pertussis in adolescents and adults. *Pediatr Infect Dis J* 2005; **24**(5 Suppl): S44-7.
6. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014; **384**(9953): 1521-8.
7. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. *Clin Infect Dis* 2017; **64**(1): 3-8.
8. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; **36**(5): 248-55.
9. Vygen-Bonnet S, Hellenbrand W, Garbe E, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. *BMC Infect Dis* 2020; **20**(1): 136.
10. Dabrera G, Amirthalingam G, Andrews N, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. *Clin Infect Dis* 2015; **60**(3): 333-7.
11. Amirthalingam G, Campbell H, Ribeiro S, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. *Clin Infect Dis* 2016; **63**(suppl 4): S236-S43.
12. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. *Pediatrics* 2017; **139**(5).
13. McMillan M, Clarke M, Parrella A, Fell DB, Amirthalingam G, Marshall HS. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. *Obstet Gynecol* 2017; **129**(3): 560-73.
14. Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA* 2014; **311**(17): 1760-9.
15. Callender M, Harvill ET. Maternal vaccination: shaping the neonatal response to pertussis. *Front Immunol* 2023; **14**: 1210580.
16. Gomme J, Wanlapakorn N, Ha HTT, Leuridan E, Herzog SA, Maertens K. The Impact of Timing of Pertussis Vaccination During Pregnancy on Infant Antibody Levels at Birth: A Multi-Country Analysis. *Front Immunol* 2022; **13**: 913922.
17. Calvert A, Amirthalingam G, Andrews N, et al. Optimising the timing of whooping cough immunisation in mums (OpTIMUM) through investigating pertussis vaccination in pregnancy: an open-label, equivalence, randomised controlled trial. *Lancet Microbe* 2023.
18. Maertens K, Orije MRP, Herzog SA, et al. Pertussis immunization during pregnancy: assessment of the role of maternal antibodies on immune responses in term and preterm born infants. *Clin Infect Dis* 2021.
19. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization. *Clin Infect Dis* 2017; **64**(8): 1129-32.
20. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *Clin Infect Dis* 2016; **62**(7): 829-36.

21. Huygen K, Cabore RN, Maertens K, Van Damme P, Leuridan E. Humoral and cell mediated immune responses to a pertussis containing vaccine in pregnant and nonpregnant women. *Vaccine* 2015; **33**(33): 4117-23.
22. Plotkin SA. Recent updates on correlates of vaccine-induced protection. *Front Immunol* 2022; **13**: 1081107.
23. Barug D, Pronk I, van Houten MA, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. *Lancet Infect Dis* 2019; **19**(4): 392-401.
24. Abu-Raya B, Giles ML, Kollmann TR, Sadarangani M. The Effect of Timing of Tetanus-Diphtheria-Acellular Pertussis Vaccine Administration in Pregnancy on the Avidity of Pertussis Antibodies. *Front Immunol* 2019; **10**: 2423.
25. Maertens K, De Schutter S, Braeckman T, et al. Breastfeeding after maternal immunisation during pregnancy: providing immunological protection to the newborn: a review. *Vaccine* 2014; **32**(16): 1786-92.
26. Nascimento RMD, Baptista PN, Lopes KAM, Pimentel AM, Cruz F, Ximenes RAA. Protective effect of exclusive breastfeeding and effectiveness of maternal vaccination in reducing pertussis-like illness. *J Pediatr (Rio J)* 2021.
27. Abu Raya B, Srugo I, Kessel A, et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels - a prospective study. *Vaccine* 2014; **32**(44): 5787-93.
28. Amirthalingam G, Campbell H, Ribeiro S, et al. Optimization of Timing of Maternal Pertussis Immunization From 6 Years of Postimplementation Surveillance Data in England. *Clin Infect Dis* 2023; **76**(3): e1129-e39.
29. Havers FP, Skoff TH, Rench MA, et al. Maternal Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccination During Pregnancy: Impact on Infant Anti-Pertussis Antibody Concentrations by Maternal Pertussis Priming Series. *Clin Infect Dis* 2023; **76**(3): e1087-e93.
30. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci U S A* 2014; **111**(2): 787-92.
31. Ciobanu AM, Dumitru AE, Gica N, Botezatu R, Peltecu G, Panaitescu AM. Benefits and Risks of IgG Transplacental Transfer. *Diagnostics (Basel)* 2020; **10**(8).
32. Balle C, Armistead B, Kiravu A, et al. Factors influencing maternal microchimerism throughout infancy and its impact on infant T cell immunity. *J Clin Invest* 2022; **132**(13).
33. Ladhani SN, Andrews NJ, Southern J, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. *Clin Infect Dis* 2015; **61**(11): 1637-44.
34. Hardy-Fairbanks AJ, Pan SJ, Decker MD, et al. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. *Pediatr Infect Dis J* 2013; **32**(11): 1257-60.
35. Abu Raya B, Edwards KM, Scheifele DW, Halperin SA. Pertussis and influenza immunisation during pregnancy: a landscape review. *Lancet Infect Dis* 2017; **17**(7): e209-e22.
36. Froberg J, van der Maas NAT, de Melker HE. [Introduction of pertussis vaccination during pregnancy]. *Ned Tijdschr Geneeskd* 2020; **164**.
37. Vaccine schedules in all countries in the EU/EEA. https://vaccine-schedule.ecdc.europa.eu/.
38. Maltezou HC, Effraimidou E, Cassimos DC, et al. Vaccination programs for pregnant women in Europe, 2021. *Vaccine* 2021; **39**(41): 6137-43.
39. Peristat. 2021. https://www.peristat.nl/.
40. Jackson ML, Yu O, Nelson JC, et al. Safety of repeated doses of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine in adults and adolescents. *Pharmacoepidemiol Drug Saf* 2018; **27**(8): 921-5.
41. Marijnen MC, Damhuis SE, Smies M, Gordijn SJ, Ganzevoort W. Practice variation in diagnosis, monitoring and management of fetal growth restriction in the Netherlands. *Eur J Obstet Gynecol Reprod Biol* 2022; **276**: 191-8.
42. Anraad C, van Keulen HM, Lehmann MA, Mollema L, van Empelen P, Ruiter RAC. Maternal pertussis vaccination: information needs and preferences for organisation among pregnant women in the Netherlands. *TSG - Tijdschrift voor gezondheidswetenschappen* 2020; **98**: 6.
43. van Lier A, Hament J, Knijff M, et al. Vaccination Coverage and Annual Report National Immunisation Programme Netherlands 2022 [in Dutch: Vaccinatiegraad en Jaarverslag

Rijksvaccinatieprogramma Nederland 2022]: National Institute for Public Health and the Environment [RIVM], 2023.
44. Pertussis vaccination programme for pregnant women update: vaccine coverage in England, April to September 2019, 2019.
45. Maertens K, Willen L, van Damme P, et al. Study of the vaccination coverage in Flanders 2020: University Antwerpen; KU Leuven, 2022.
46. Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022-23 Influenza Season. *MMWR Recomm Rep* 2022; **71**(1): 1-28.
47. Vaccine update: issue 344, November 2023, pregnancy special, 2023.
48. Gauld N, Martin S, Sinclair O, Petousis-Harris H, Dumble F, Grant CC. Influences on Pregnant Women's and Health Care Professionals' Behaviour Regarding Maternal Vaccinations: A Qualitative Interview Study. *Vaccines (Basel)* 2022; **10**(1).
49. Flu vaccination: revision of the indication 2021, 2021.
50. Pluijmaekers AJM, de Melker H. The National Immunisation Programme in the Netherlands: Surveillance and Developments in 2021-2022: National Institute for Public Health and the Environment (RIVM), 2022.
51. Callahan AG, Strassberg ER, Rhoades CP, Varghese L, Schulkin J, Power ML. Pregnant Women's Opinions and Acceptance of Influenza and Tdap Vaccines. *J Womens Health (Larchmt)* 2022; **31**(5): 656-64.
52. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet* 2022; **399**(10340): 2047-64.
53. Wildenbeest JG, Billard MN, Zuurbier RP, et al. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. *Lancet Respir Med* 2023; **11**(4): 341-53.
54. First RSV vaccine to protect infants up to 6 months of age and older adults. 2023. https://www.ema.europa.eu/en/news/first-rsv-vaccine-protect-infants-6-months-age-older-adults.
55. FDA Approves First Vaccine for Pregnant Individuals to Prevent RSV in Infants. 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants.
56. Preferred Product Characteristics for Respiratory Syncytial Virus (RSV) Vaccines: World Health Organization (WHO), 2017.
57. New medicine to protect babies and infants from respiratory syncytial virus (RSV) infection. 2022. https://www.ema.europa.eu/en/news/new-medicine-protect-babies-infants-respiratory-syncytial-virus-rsv-infection.
58. FDA Approves New Drug to Prevent RSV in Babies and Toddlers. 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-prevent-rsv-babies-and-toddlers.
59. Werkagenda advisering Vaccinaties Gezondheidsraad 2023. https://www.rijksoverheid.nl/documenten/publicaties/2023/03/21/werkagenda-advisering-vaccinaties-gezondheidsraad-2023.
60. Passive immunoprophylaxis with Palivizumab, 2022.
61. Bont L. Preventie en behandeling van RSV-bronchiolitis. *Infectieziekten Bulletin* 2016; **27**(6).
62. Middeldorp M, van Lier A, van der Maas N, et al. Short term impact of the COVID-19 pandemic on incidence of vaccine preventable diseases and participation in routine infant vaccinations in the Netherlands in the period March-September 2020. *Vaccine* 2021; **39**(7): 1039-43.

Appendices

Maternale vaccinatie tegen kinkhoest in het Rijksvaccinatieprogramma: evaluatie onder verloskundig zorgverleners één jaar na de implementatie in december 2019

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Samenvatting

Inleiding en doel

Eind 2019 is de maternale kinkhoestvaccinatie opgenomen in het Rijksvaccinatieprogramma. Verloskundig zorgverleners brengen de vaccinatie bij zwangere vrouwen onder de aandacht en verwijzen hen naar de Jeugdgezondheidszorg voor vragen en het toedienen van de vaccinatie. De attitude van de verloskundig zorgverlener t.a.v. de maternale kinkhoestvaccinatie is voor zwangere vrouwen belangrijk in het besluit om zich te laten vaccineren. Het doel van deze studie was om inzicht te krijgen in attitudes van verloskundig zorgverleners en welke factoren daarop van invloed zijn.

Methode

In deze cross-sectionele studie verspreidde het RIVM een vragenlijst via beroepsorganisaties van verloskundig zorgverleners. Zij beantwoordden vragen over de maternale kinkhoestvaccinatie: communicatie met zwangere vrouwen, communicatie met de Jeugdgezondheidszorg, onderwerpen waarover zwangere vrouwen vragen stellen en attitudes van verloskundig zorgverleners. Voorspellende factoren op attitude t.a.v. de maternale kinkhoestvaccinatie werden geïdentificeerd middels lineaire regressiemethoden.

Resultaten

Van de 5.215 uitgenodigde verloskundig zorgverleners beantwoordden 817 eerstelijns- en 35 klinisch verloskundigen, 55 arts-assistenten en 146 gynaecologen de vragenlijst (20%). 39% van de verloskundig zorgverleners overhandigde het complete informatiemateriaal, bestaande uit een brief en folder, aan zwangere vrouwen. Gemiddelde attitude t.a.v. de maternale kinkhoestvaccinatie was 4 (schaal van 1-5). Deze attitude hing samen met een positieve attitude t.a.v. het Rijksvaccinatieprogramma ($p<0,0001$), het volgen van de e-learning ($p<0,001$), zich bekwaam voelen om zwangere vrouwen te informeren ($p<0,0001$) en de beroepsgroep van arts-assistenten/gynaecologen t.o.v. verloskundigen ($p<0,0001$).

Conclusie

Verloskundig zorgverleners waren overwegend positief over de maternale kinkhoestvaccinatie. (Online) trainingen aan verloskundig zorgverleners dragen mogelijk bij aan een positieve attitude t.a.v. de maternale kinkhoestvaccinatie. Samenwerking tussen verloskundig zorgverleners en de Jeugdgezondheidszorg en het meegeven van informatiematerialen aan zwangere vrouwen kunnen worden verbeterd.

Inleiding

Kinkhoest is een zeer besmettelijke respiratoire infectieziekte die meestal wordt veroorzaakt door de bacterie *Bordetella pertussis*. Jonge (nog niet volledig gevaccineerde) zuigelingen hebben een verhoogd risico op een ernstig ziektebeloop, met als gevolg ziekenhuisopname en soms sterfte.[1] Sinds de jaren 90 komt kinkhoest in Nederland en andere landen ondanks een hoge vaccinatiegraad weer vaker voor met elke 3 tot 4 jaar een piek in landelijke incidentiecijfers.[2,3] In 2012 was in Nederland en omringende landen gedurende lange tijd sprake van een flinke stijging van het aantal meldingen van kinkhoest. In het Verenigd Koninkrijk is toen besloten om vrouwen in het derde trimester van de zwangerschap een vaccinatie tegen kinkhoest aan te bieden. Deze *maternale kinkhoestvaccinatie* zorgt voor passieve immuniteit bij de baby in de eerste maanden na de geboorte, als gevolg van transplacentaire IgG-antistofoverdracht. Hierdoor is de baby goed beschermd tegen kinkhoest totdat het de eerste eigen vaccinatie krijgt.[4] Het Verenigd Koninkrijk bereikte met deze strategie een vaccinatiegraad van ongeveer 70%; de vaccineffectiviteit was ruim 90%.[5]

In Nederland heeft de Gezondheidsraad in 2015 geadviseerd om vrouwen een kinkhoestvaccinatie aan te bieden in het derde trimester van de zwangerschap.[6] Vrouwen konden toen op eigen initiatief gevaccineerd worden bij de GGD, huisarts, verloskundige of gynaecoloog. In de periode 2018-2019 lieten steeds meer zwangere vrouwen zich vaccineren.[7] Halverwege december 2019 werd de maternale kinkhoestvaccinatie opgenomen in het Rijksvaccinatieprogramma (RVP) en is sindsdien bekend als *de 22-wekenprik* die gegeven wordt als difterie-kinkhoest-tetanus (DKT-)vaccinatie.[8] De maternale kinkhoestvaccinatie vervangt ook de eerste vaccinatie van het kind, dat vervolgens wordt gevaccineerd volgens een 3-5-11-maandenschema, in plaats van een 2-3-5-11-maandenschema. Er zijn enkele uitzonderingen op het standaard vaccinatieschema, zoals bij kinderen die te vroeg geboren zijn (< 37 weken) of kinderen van wie de moeder minder dan 2 weken voor de bevalling is gevaccineerd.[9] Deze kinderen worden gevaccineerd volgens het 2-3-5-11-maanden schema.

Sinds de opname van de maternale kinkhoestvaccinatie in het RVP krijgen zwangere vrouwen de vaccinatie bij de Jeugdgezondheidszorg (JGZ). Het advies aan zwangere vrouwen is om deze zo snel mogelijk vanaf 22 weken zwangerschapsduur te halen. Op dat moment is de 20-wekenecho al gemaakt, waardoor er een goed uitgangspunt is voor het monitoren van de groei en ontwikkeling van het kind. Het is aan verloskundig zorgverleners om de maternale kinkhoestvaccinatie bij de zwangere vrouw onder de aandacht te brengen. De zorgverlener overhandigt een envelop met daarin een brief en een folder van het

Rijksinstituut voor Volksgezondheid en Milieu (RIVM) met informatie over de maternale kinkhoestvaccinatie en verwijst de zwangere vrouw naar de JGZ. De JGZ beantwoordt eventuele vragen en dient, indien gewenst, het vaccin toe.[10]

Zwangere vrouwen stellen hun vragen over de maternale kinkhoestvaccinatie regelmatig aan hun verloskundig zorgverlener, huisarts of andere specialist. Wat een zorgverlener vindt van de vaccinatie (*attitude)* is voor zwangere vrouwen één van de belangrijkste factoren die meeweegt in de beslissing om zich wel of niet te laten vaccineren.[11-16] Het Rijksinstituut voor Volksgezondheid en Milieu heeft deze studie uitgevoerd om inzicht te krijgen in de attitude ten aanzien van de maternale kinkhoestvaccinatie onder verloskundig zorgverleners nadat de vaccinatie werd opgenomen in het RVP.

Methoden

Setting

In november 2020 ontvingen eerstelijnsverloskundigen, klinisch verloskundigen, arts-assistenten gynaecologie en gynaecologen via hun beroepsverenigingen – de Koninklijke Nederlandse Organisatie van Verloskundigen (KNOV) en de Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) - per e-mail een link naar een vragenlijst. Zij hadden vier weken de tijd om de vragenlijst in te vullen.

Uitkomsten

Verloskundig zorgverleners beantwoordden gesloten vragen over onderwerpen rondom de maternale kinkhoestvaccinatie: communicatie met zwangere vrouwen, communicatie met de JGZ, onderwerpen waarover zwangere vrouwen vragen stellen en attitudes van verloskundig zorgverleners. Attitudes van de respondenten werden uitgevraagd in theoretische constructen, gemeten aan de hand van drie stellingen (items) die gezamenlijk het construct reflecteerden. De items werden gemeten op een 5-punts Likertschaal (kader 1). Attitude werd gedefinieerd als de mate waarin een persoon een gunstige of ongunstige houding ten aanzien van de stelling in kwestie had.[17]

Statistische analyse

De uitkomst van elk construct werd berekend als gemiddelde somscore van alle items binnen hetzelfde construct, mits deze items voldoende betrouwbaar bij elkaar pasten (de interne consistentie was voldoende bij een Cronbach's α van >0,60). Variabelen die van invloed waren op de attitude ten aanzien van de maternale kinkhoestvaccinatie werden geanalyseerd door middel van lineaire

regressie en geselecteerd voor stapsgewijze achterwaartse multivariabele lineaire regressie bij een p-waarde <0,10. Variabelen met een p-waarde van <0,05 in de multivariabele analyse werden beschouwd als significante voorspellers van attitude en gepresenteerd als gecorrigeerde β met corresponderend 95% betrouwbaarheidsinterval (BI).

Kader 1. Constructen en voorbeeldstellingen binnen elk construct.

Construct	Voorbeeldstelling
Attitude t.a.v. de maternale kinkhoestvaccinatie	Dat zwangere vrouwen de 22-wekenprik nemen vind ik: *(1 = heel erg onbelangrijk, 5 = heel erg belangrijk)*
Attitude t.a.v. het RVP	Dat kinderen het Rijksvaccinatieprogramma volgen vind ik: *(1 = heel erg onnodig, 5 = heel erg nodig)*
Bekwaamheid in het informeren van zwangere vrouwen	Inhoudelijke informatie geven aan zwangere vrouwen over de 22-wekenprik: *(1 = voel ik mij erg onzeker over, 5 = voel ik mij erg zeker over*)

Resultaten

In totaal werden 5.215 verloskundig zorgverleners uitgenodigd om deel te nemen aan dit onderzoek; 3.716 verloskundigen en 1.499 arts-assistenten gynaecologie of gynaecologen. De vragenlijst werd ingevuld door 817 eerstelijnsverloskundigen, 35 klinisch verloskundigen, 146 gynaecologen en 55 arts-assistenten (tabel 1). Daarmee hebben 23% van de eerstelijns- en klinisch verloskundigen en 13% van de arts-assistenten of gynaecologen gereageerd.

Communicatie met zwangere vrouwen

Bijna alle respondenten (98%) gaven aan dat zij de mogelijkheid van de maternale kinkhoestvaccinatie bespreken met zwangere vrouwen. 62% deed dat op een moment in de eerste 18 weken van de zwangerschap. 39% van de respondenten gaf de complete set informatiemateriaal mee, namelijk de folder en de brief van het RIVM. 43% gaf alleen de folder mee en 11% gaf alleen de brief mee. De overige 7% gaf geen informatiemateriaal van het RIVM mee. 1% van de respondenten gaf aan dat zij, naast het overhandigen van informatiemateriaal, zwangere vrouwen ook wijzen op meer kritische informatie over vaccineren.

Tabel 1. Demografische gegevens van verloskundige zorgverleners en uitgevraagde aspecten rondom de maternale kinkhoestvaccinatie.

	Eerstelijns verloskundige n=817 (77,6%)	**Klinisch verloskundige n=35 (3,3%)**	**Gynaecoloog of arts-assistent n=201 (19,1%)**	**Totaal n=1.053 (100,0%)**
Vaccinatie besproken	810 (99,1)	30 (85,7)	187 (93,0)	1027 (97,5)
E-learning gevolgd				
Ja	292 (35,7)	14 (40,0)	36 (17,9)	342 (32,5)
Nee	442 (54,1)	20 (57,1)	152 (75,6)	614 (58,3)
Onbekend	83 (10,2)	1 (2,9)	13 (6,5)	97 (9,2)
Overhandigd materiaal[a]				
Folder RIVM	673 (82,4)	29 (82,9)	156 (77,6)	858 (81,5)
Brief RIVM	471 (57,6)	6 (17,1)	47 (23,4)	524 (49,8)
Informatie van JGZ	126 (15,4)	3 (8,6)	16 (8,0)	145 (13,8)
Overige informatie	83 (10,2)	8 (22,9)	23 (11,4)	114 (10,8)
Geen	2 (0,2)	0 (0,0)	9 (4,5)	11 (1,0)
Moment van informatieverstrekking[b]				
Tot 18w zwangerschapsduur	530 (64,9)	16 (45,7)	110 (54,7)	656 (62,3)
Vanaf 18w zwangerschapsduur	280 (34,0)	14 (40,0)	73 (36,3)	366 (34,8)
Tijdsinvestering				
0-5 minuten	624 (76,4)	34 (97,1)	191 (95,0)	849 (80,6)
6 minuten of langer	193 (23,6)	1 (2,9)	10 (5,0)	204 (19,4)

Tabel 1. Vervolgd

	Eerstelijns verloskundige n=817 (77,6%)	Klinisch verloskundige n=35 (3,3%)	Gynaecoloog of arts-assistent n=201 (19,1%)	Totaal n=1.053 (100,0%)
Tevreden over huidige werkwijze				
Ja	439 (53,7)	26 (74,3)	167 (83,1)	632 (60,0)
Nee	212 (25,9)	3 (8,6)	9 (4,5)	224 (21,3)
Gedeeltelijk	166 (20,3)	6 (17,1)	25 (12,4)	197 (18,7)
Poster in wachtkamer				
Ja	483 (59,1)	20 (57,1)	130 (64,7)	633 (60,1)
Nee	272 (33,3)	13 (37,1)	64 (31,8)	349 (33,1)
Alleen vroeger	62 (7,6)	2 (5,7)	7 (3,5)	71 (6,7)
Vraagt na of de vaccinatie gehaald is				
Ja	625 (76,5)	23 (65,7)	134 (66,7)	782 (74,3)
Nee	65 (8,0)	0 (0,0)	17 (8,5)	82 (7,8)
Soms	127 (15,5)	12 (34,3)	50 (24,9)	189 (17,9)
JGZ geeft zorgverlener melding van toegediend vaccin				
Soms, vaak of altijd	41 (5,0)	0 (0,0)	2 (1,0)	43 (4,1)
Nooit tot weinig	757 (92,7)	24 (68,6)	103 (51,2)	884 (84,0)
Onbekend	19 (2,3)	11 (31,4)	96 (47,8)	126 (12,0)

Tabel 1. Vervolgd

	Eerstelijns verloskundige n=817 (77,6%)	Klinisch verloskundige n=35 (3,3%)	Gynaecoloog of arts-assistent n=201 (19,1%)	Totaal n=1.053 (100,0%)
JGZ geeft zorgverlener melding van toegediend vaccin				
Soms, vaak of altijd	41 (5,0)	0 (0,0)	2 (1,0)	43 (4,1)
Nooit tot weinig	757 (92,7)	24 (68,6)	103 (51,2)	884 (84,0)
Onbekend	19 (2,3)	11 (31,4)	96 (47,8)	126 (12,0)
Zorgverlener wenst terugkoppeling van de JGZ	395 (48,5)	15 (42,9)	90 (44,8)	501 (47,6)
Hoeveelheid gekregen vragen over onderwerpen; gemiddelde score (sd); 1 = geen vragen, 5 = heel veel vragen				
Praktisch	4,1 (1,0)	3,7 (1,1)	3,8 (1,1)	4,1 (1,0)
Veiligheid voor het kind	3,9 (1,1)	3,2 (1,3)	3,5 (1,2)	3,8 (1,1)
Waarom de vaccinatie wordt aangeboden	3,5 (1,2)	2,8 (1,3)	2,9 (1,3)	3,3 (1,2)
Veiligheid voor de moeder	3,1 (1,2)	2,5 (1,2)	2,7 (1,2)	3,0 (1,2)
Hoe de vaccinatie werkt	2,8 (1,3)	2,1 (1,1)	2,1 (1,1)	2,7 (1,3)
Effectiviteit van het vaccin	2,7 (1,3)	2,3 (1,3)	2,3 (1,1)	2,6 (1,2)

sd, standaarddeviatie; JGZ, Jeugdgezondheidszorg. [a] aantallen overhandigd materiaal tellen niet op tot 100% omdat verloskundig zorgverleners meerdere antwoorden konden invullen. [b] 31 respondenten missen omdat zij geen zwangere vrouwen counselden over de maternale kinkhoestvaccinatie.

Communicatie met de JGZ

98% van de respondenten gaf aan dat de mate van contact met de JGZ onveranderd is sinds de implementatie van de maternale kinkhoestvaccinatie. 84% ontving geen bevestiging van JGZ over een toegediend vaccin van één van hun cliënten of patiënten, 4% ontving wel of regelmatig een bevestiging en overige 12% wist dat niet; het melden van een toegediend vaccin is echter tot op heden geen onderdeel van de richtlijn. 48% van de respondenten gaf aan wel een bevestiging te willen ontvangen.

Onderwerpen waarover zwangere vrouwen vragen stellen

De meeste vragen van de vrouwen gingen over hoe zij de vaccinatie kunnen krijgen (gemiddelde score 4,1 op een schaal van 1 tot 5) en over de veiligheid van het vaccin met betrekking tot hun ongeboren kind (gemiddelde score 3,8 op een schaal van 1 tot 5). Ten opzichte van deze onderwerpen stellen zij relatief weinig vragen over de effectiviteit van de vaccinatie (gemiddelde score 2,6 op een schaal van 1 tot 5). Aan eerstelijns- en klinisch verloskundigen werden meer vragen gesteld dan aan arts-assistenten of gynaecologen ($p<0,0001$). Het totale aantal vragen over de verschillende onderwerpen was echter naar verhouding gelijk verdeeld over de verschillende verloskundige disciplines ($p=0,02$; Spearman's $r=0,94$).

Attitudes van verloskundig zorgverleners en factoren die daarop van invloed zijn

De items binnen de theoretische constructen werden beoordeeld als voldoende consistent (Cronbach's α tussen 0,86-0,96). De gemiddelde attitude van eerstelijnsverloskundigen ten aanzien van de maternale kinkhoestvaccinatie was 3,8 op een schaal van 1 tot 5 (0,82 standaarddeviaties (sd)), 4,0 (0,76 sd) onder klinisch verloskundigen en 4,4 (0,61 sd) onder arts-assistenten en gynaecologen. Arts-assistenten en gynaecologen waren daarmee positiever gestemd over de maternale kinkhoestvaccinatie dan eerstelijnsverloskundigen (gecorrigeerde $\beta=0,27$, 95% BI 0,18-0,37) en klinisch verloskundigen (gecorrigeerde $\beta=0,32$, 95% BI 0,10-0,53) (tabel 2). Degenen die positief waren over de vaccinatie waren vaak ook positief over het totale RVP (gecorrigeerde $\beta=0,66$, 95% BI 0,61-0,72), hadden zij vaker de e-learning over de maternale kinkhoestvaccinatie gevolgd (gecorrigeerde $\beta=0,17$, 95% BI 0,09-0,25) en voelden zij zich meer bekwaam om de vrouwen te informeren over de maternale kinkhoestvaccinatie (gecorrigeerde $\beta=0,14$, 95% BI 0,09-0,18).

Tabel 2. Uni- en multivariabele lineaire regressie analyse van voorspellende factoren op de attitude t.a.v. de maternale kinkhoestvaccinatie onder verloskundige zorgverleners.

Potentieel voorspellende factor op attitude t.a.v. van de maternale kinkhoestvaccinatie	n (totaal = 1.053)	Gemiddelde attitude (sd)	Univariabele ruwe β (95% BI)	p-waarde	Multivariabele gecorrigeerde β (95% BI)	p-waarde
Type zorgverlener				<0,0001		<0,0001
Eerstelijns verloskundige	817	3,84 (0,82)	Ref.		Ref.	
Klinisch verloskundige	35	3,98 (0,76)	0,14 (-0,12-0,41)		-0,05 (-0,25-0,15)	
Gynaecoloog of arts-assistent	201	4,39 (0,61)	0,56 (0,44-0,68)		0,27 (0,17-0,37)	
E-learning gevolgd				0,026		<0,001
Ja	342	4,04 (0,81)	0,12 (0,02-0,23)		0,17 (0,09-0,25)	
Nee	614	3,92 (0,81)	Ref.		Ref.	
Onbekend	97	3,83 (0,78)	-0,08 (-0,26-0,09)		0,01 (-0,12-0,14)	
Moment van informatieverstrekking				0,843		
Tot 18w zwangerschapsduur	656	3,96 (0,78)	0,02 (-0,08-0,12)			
Vanaf 18w zwangerschapsduur	366	3,94 (0,85)	Ref.			
N.v.t.[a]	31	3,88 (0,98)	-0,06 (-0,35-0,24)			

Tabel 2. Vervolgd.

Potentieel voorspellende factor op attitude t.a.v. van de maternale kinkhoestvaccinatie	n (totaal = 1.053)	Gemiddelde attitude (sd)	Univariabele ruwe β (95% BI)	p-waarde	Multivariabele gecorrigeerde β (95% BI)	p-waarde
Tijdsinvestering				0,495		
5 minuten of minder	849	3,96 (0,79)	0,04 (-0,08-0,17			
Meer dan 5 minuten	204	3,91 (0,87)	Ref.			
Poster in wachtkamer				<0,001		
Ja	633	4,03 (0,78)	0,22 (0,11-0,32)			
Nee	349	3,81 (0,84)	Ref.			
Alleen vroeger	71	3,87 (0,87)	0,06 (-0,15-0,26)			
Vraagt na of de vaccinatie gehaald is				0,001		
Ja	782	4,00 (0,78)	0,28 (0,10-0,47)			
Nee	82	3,72 (0,83)	Ref.			
Soms	189	3,84 (0,89)	0,12 (-0,08-0,33)			
Bekwaamheid in het informeren van zwangere vrouwen	N.v.t.	N.v.t.	0,25 (0,19-0,31)	<0,0001	0,13 (0,09-0,18)	<0,0001
Attitude t.a.v. het RVP	N.v.t.	N.v.t.	0,72 (0,67-0,78)	<0,0001	0,66 (0,61-0,72)	<0,0001

BI, betrouwbaarheidsinterval; ref., referentie; RVP, rijksvaccinatieprogramma; sd, standaarddeviatie. [a] 31 respondenten missen omdat zij geen zwangere vrouwen counselden over de maternale kinkhoestvaccinatie.

Discussie

De verloskundig zorgverleners in dit onderzoek waren overwegend positief over de maternale kinkhoestvaccinatie. Zij bespraken de vaccinatie bijna allemaal met de zwangere vrouwen, met als doel hen te doen besluiten zich te laten vaccineren. De verloskundig zorgverleners die positief waren tegenover de vaccinatie hadden over het algemeen meer vertrouwen in het RVP, hadden vaker de e-learning over de maternale kinkhoestvaccinatie gevolgd en voelden zich meer bekwaam om vrouwen te informeren over de vaccinatie. Net als in andere landen stonden arts-assistenten en gynaecologen positiever tegenover de maternale kinkhoestvaccinatie dan de eerstelijns- en klinisch verloskundigen.[11,18] Uit andere onderzoeken blijkt dat zwangere vrouwen vaker geneigd zijn zich te laten vaccineren tegen kinkhoest als hun zorgverlener daar positief tegenover staat.[11-16] Hoewel er in deze studie geen causaal verband kon worden aangetoond, lijkt het erop dat de positieve houding van verloskundig zorgverleners onder meer samenhangt met de mate van kennis die zij hebben over de maternale kinkhoestvaccinatie. Ook in andere studies is dit aangetoond.[15,19] Om de kennis van verloskundig zorgverleners over de maternale kinkhoestvaccinatie te vergroten, is het belangrijk om hen regelmatig op de hoogte te houden van nieuwe ontwikkelingen en om (online) trainingen (zoals de e-learning) meer te promoten. De e-learning wordt weliswaar al aan alle verloskundig zorgverleners aangeboden, maar uit de huidige studie blijkt dat slechts ongeveer een derde van hen deze training heeft gevolgd. Omdat ook huisartsen en andere specialisten door zwangere vrouwen vaak als vertrouwenspersoon worden gezien,[20,21] zouden de medische beroepsgroepen die regelmatig te maken krijgen met de maternale kinkhoestvaccinatie regelmatig moeten worden geïnformeerd en geattendeerd op (online) trainingen. Uiteindelijk verwachten we dat deze interventies ertoe zullen leiden dat meer vrouwen zich tijdens de zwangerschap laten vaccineren tegen kinkhoest.

Naast de mening van de zorgverlener over de vaccinatie, zijn de mate van veiligheid en effectiviteit van de maternale kinkhoestvaccinatie ook van invloed op de vaccinatiebereidheid onder zwangere vrouwen.[22-25] Verloskundig zorgverleners gaven aan dat zij voornamelijk vragen krijgen over de veiligheid en in mindere mate over de effectiviteit. De effectiviteit van de vaccinatie zou daarom actiever besproken kunnen worden op initiatief van de zorgverlener of bij de JGZ.

Een klein deel van de verloskundig zorgverleners gaf de complete set aan informatiemateriaal (i.e. informatiebrief en folder van het RIVM) mee aan zwangere vrouwen, zodat zwangere vrouwen zich kunnen melden bij de JGZ voor de vaccinatie. Wel hebben zij vaak de wens om van de JGZ een bevestiging te

ontvangen na een toegediend vaccin. Dit suggereert dat er weinig tot geen inhoudelijk contact is tussen verloskundig zorgverleners en de JGZ over de maternale kinkhoestvaccinatie, maar dat de zorgverleners dat wel graag zouden willen. Een evaluatie over de maternale kinkhoestvaccinatie bij JGZ-medewerkers bevestigt deze behoefte tot samenwerking vanuit de JGZ.[26] De evaluatie vermeldt ook het advies aan de KNOV en NVOG om een sterker standpunt in te nemen over het contact tussen verloskundig zorgverleners en de JGZ rondom de maternale kinkhoestvaccinatie. Mogelijk kunnen meer zwangere vrouwen worden bereikt met deze strategie.

Er zijn enkele beperkingen aan deze studie. Allereerst is er mogelijk sprake van selectiebias. Wellicht was een selectief deel van verloskundig zorgverleners eerder geneigd om de vragenlijst in te vullen.(27) Het zou echter ook kunnen dat zowel verloskundig zorgverleners met een positieve ofwel een negatieve attitude relatief vaker de vragenlijst hebben ingevuld, wat de effecten van selectiebias mogelijk in balans houdt. Daarom is deze eventuele selectieve deelname naar verwachting weinig van invloed bij het benaderen van de werkelijke attitude. Uit andere studies komen dan ook vergelijkbare resultaten naar voren als uit het huidige onderzoek, zoals de positieve attitude onder gynaecologen.(11, 18) Ten tweede deden aan dit onderzoek alleen zorgverleners mee die verloskundige zorg leveren. Huisartsen en andere specialisten hebben echter ook regelmatig te maken met de maternale kinkhoestvaccinatie. Daarom zou vervolgonderzoek bij andere medische beroepsgroepen meer inzicht geven de attitude van deze beroepsgroepen ten aanzien van de maternale kinkhoestvaccinatie. Met dergelijk vervolgonderzoek kan ook onderzocht worden wat het effect is van de attitude van de zorgverlener op het accepteren van het vaccin door zwangere vrouwen in Nederland. Als laatste zijn er mogelijk nuances die de respondenten niet naar voren hebben kunnen brengen via de kwantitatieve vragenlijst. Daarom zal dit onderzoek worden vervolgd met een kwalitatieve studie. Hierdoor probeert het RIVM inzicht te krijgen in de context rondom de implementatie van de maternale kinkhoestvaccinatie. Dat biedt mogelijk ook suggesties voor verbetering wanneer maternale vaccinaties gericht tegen andere pathogenen worden opgenomen in het RVP.

Conclusie

Verloskundig zorgverleners – en dan vooral gynaecologen en arts-assistenten gynaecologie – staan overwegend positief tegenover de maternale kinkhoestvaccinatie. Hoe positiever zij zijn, des te meer vertrouwen zij hebben in het totale RVP, achten zij zich bekwaam om zwangere vrouwen over de vaccinatie te informeren en hebben zij de e-learning over de maternale kinkhoestvaccinatie

gevolgd. Deze e-learning zou actiever en breder kunnen worden aangeboden; aan zowel verloskundig zorgverleners als huisartsen en andere specialisten. Verdere verbeterpunten zijn de versterking van de samenwerking tussen verloskundig zorgverleners en de JGZ, en het meegeven van informatiematerialen aan de zwangere vrouwen.

Referenties

1. Vegelin AL, van Vught AJ, Wolfs TF, Kimpen JL, Geelen SP. [Pertussis in young infants]. *Ned Tijdschr Geneeskd* 1998; **142**(49): 2657-60.
2. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. *Emerg Infect Dis* 2000; **6**(4): 348-57.
3. van der Maas NA, Mooi FR, de Greeff SC, Berbers GA, Spaendonck MA, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? *Vaccine* 2013; **31**(41): 4541-7.
4. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. *Clin Infect Dis* 2017; **64**(1): 3-8.
5. Amirthalingam G, Campbell H, Ribeiro S, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. *Clin Infect Dis* 2016; **63**(suppl 4): S236-S43.
6. Dossier vaccinatie tegen kinkhoest: doel en strategie. 2015. https://www.gezondheidsraad.nl/documenten/adviezen/2015/12/02/vaccinatie-kinkhoest-doel-en-strategie.
7. Schurink-van 't Klooster TM, de Melker HE. The National Immunisation Programme in the Netherlands - Surveillance en Developments in 2019-2020, 2020.
8. 22-wekenprik. 2019. https://rijksvaccinatieprogramma.nl/22wekenprik.
9. Froberg J, van der Maas NAT, de Melker HE. [Introduction of pertussis vaccination during pregnancy]. *Ned Tijdschr Geneeskd* 2020; **164**.
10. Richtlijn Uitvoering RVP 2021. 2020. https://rijksvaccinatieprogramma.nl/documenten/rvp-richtlijn-uitvoering-rvp-2020 (accessed 15 februari 2021.
11. Maertens K, Braeckman T, Top G, Van Damme P, Leuridan E. Maternal pertussis and influenza immunization coverage and attitude of health care workers towards these recommendations in Flanders, Belgium. *Vaccine* 2016; **34**(47): 5785-91.
12. Anraad C, Lehmann BA, Visser O, et al. Social-psychological determinants of maternal pertussis vaccination acceptance during pregnancy among women in the Netherlands. *Vaccine* 2020; **38**(40): 6254-66.
13. Vishram B, Letley L, Jan Van Hoek A, et al. Vaccination in pregnancy: Attitudes of nurses, midwives and health visitors in England. *Hum Vaccin Immunother* 2018; **14**(1): 179-88.
14. Robbins SC, Leask J, Hayles EH, Sinn JK. Midwife attitudes: an important determinant of maternal postpartum pertussis booster vaccination. *Vaccine* 2011; **29**(34): 5591-4.
15. Regan AK, Hauck Y, Nicolaou L, et al. Midwives' knowledge, attitudes and learning needs regarding antenatal vaccination. *Midwifery* 2018; **62**: 199-204.
16. Moniz MH, Vitek WS, Akers A, Meyn LA, Beigi RH. Perceptions and acceptance of immunization during pregnancy. *J Reprod Med* 2013; **58**(9-10): 383-8.
17. Ajzen I. The theory of planned behavior. *Organizational Behavior and Human Decision Processes* 1991; **50**(2): 179-211.
18. Dube E, Gagnon D, Kaminsky K, et al. Vaccination during pregnancy: Canadian maternity care providers' opinions and practices. *Hum Vaccin Immunother* 2020; **16**(11): 2789-99.
19. Vilca LM, Martinez C, Burballa M, Campins M. Maternal Care Providers' Barriers Regarding Influenza and Pertussis Vaccination During Pregnancy in Catalonia, Spain. *Matern Child Health J* 2018; **22**(7): 1016-24.
20. Croker JE, Swancutt DR, Roberts MJ, Abel GA, Roland M, Campbell JL. Factors affecting patients' trust and confidence in GPs: evidence from the English national GP patient survey. *BMJ Open* 2013; **3**(5).
21. E-learning Maternale kinkhoestvaccinatie. https://www.nspoh.nl/e-learning-maternale-kinkhoestvaccinatie/.
22. Varan AK, Esteves-Jaramillo A, Richardson V, Esparza-Aguilar M, Cervantes-Powell P, Omer SB. Intention to accept Bordetella pertussis booster vaccine during pregnancy in Mexico City. *Vaccine* 2014; **32**(7): 785-92.
23. Hill L, Burrell B, Walls T. Factors influencing women's decisions about having the pertussis-containing vaccine during pregnancy. *J Prim Health Care* 2018; **10**(1): 62-7.

24. Hayles EH, Cooper SC, Sinn J, Wood N, Leask J, Skinner SR. Pertussis vaccination coverage among Australian women prior to childbirth in the cocooning era: a two-hospital, cross-sectional survey, 2010 to 2013. *Aust N Z J Obstet Gynaecol* 2016; **56**(2): 185-91.
25. Ko HS, Jo YS, Kim YH, et al. Knowledge and Acceptability about Adult Pertussis Immunization in Korean Women of Childbearing Age. *Yonsei Med J* 2015; **56**(4): 1071-8.
26. Pluijmaekers AJM, Hament JM. Evaluatie Maternale Kinkhoest. Van implementatie tot uitvoering bij de JGZ: Rijksinstituut voor Volksgezondheid en Milieu (RIVM), 2021.

Appendices

Nederlandse samenvatting

Introductie

In dit proefschrift bestuderen we verschillende aspecten van de vaccinatie tegen kinkhoest bij zwangere vrouwen ter bescherming van pasgeborenen in de eerste twee tot drie levensmaanden. Hiervoor vergelijken we een vroeger in de zwangerschap gegeven tetanus, difterie en acellulaire kinkhoest (DKT) vaccinatie tussen $20^{0/7}$-$24^{0/7}$ weken (w) zwangerschapsduur met een DKT-vaccinatie later in de zwangerschap, namelijk tussen $30^{0/7}$-$33^{0/7}$w zwangerschapsduur. Behalve de vergelijking van de hoeveelheid antistoffen die wordt doorgegeven van moeder naar kind, wordt ook de acceptatie van de DKT-vaccinatie rond de 22 weken vergeleken met vaccinatie rond de 30-33 weken. Voor dit doel is een groot longitudinaal cohortonderzoek opgezet getiteld '**P**remature **I**nfants and **M**aternal **P**ertussis **I**mmunization' (PIMPI). De studie was gericht op drie belangrijke vraagstellingen over maternale DKT-vaccinatie vóór 24 weken zwangerschapsduur; 1) Wat zijn de kinkhoest-specifieke antistofconcentraties bij voldragen (à terme) kinderen en te vroeg (prematuur) geboren kinderen na een vroege maternale DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur, vergeleken met vaccinatie tussen $30^{0/7}$-$33^{0/7}$w zwangerschapsduur?; 2) Wat zijn de acute bijwerkingen (reactogeniciteit) van maternale DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur?; en 3) Wat is de acceptatie van maternale DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur door zwangere vrouwen?

De PIMPI-studie is relevant omdat een grote groep prematuur geboren kinderen is geïncludeerd, waar nog relatief weinig gegevens over beschikbaar zijn, zeker als het gaat om maternale DKT-vaccinatie voor 24 weken zwangerschapsduur. Bovendien zijn ook over voldragen kinderen weinig data beschikbaar met betrekking tot DKT-vaccinatie vóór 24 weken. De resultaten van beide groepen, prematuur en voldragen kinderen, worden beschreven in dit proefschrift.

De PIMPI-studie heeft zich specifiek gericht op de mogelijke voordelen van DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur voor te vroeg geboren kinderen. In de studie is 'prematuur' gedefinieerd als geboren vóór $35^{0/7}$w zwangerschapsduur, terwijl meestal wordt over premature geboorte gesproken wanneer de geboorte vóór 37 weken is. Maar omdat de concentraties van maternale antistoffen die tijdens de zwangerschap van moeder naar kind worden doorgegeven rond de 35 weken zwangerschapsduur al vergelijkbaar zijn tussen moeder en kind, is in dit onderzoek vooral naar kinderen gekeken die werden geboren vóór 35 weken. De studie beoogde niet alleen om een grote groep prematuur geboren kinderen voor 35 weken zwangerschapsduur te includeren, maar vooral ook prematuur geborenen voor 32 weken zwangerschapsduur. Met

name voor deze vroege prematuren zijn data buitengewoon schaars, zeker in geval van maternale DKT-vaccinatie voor 24 weken zwangerschapsduur. De resultaten van de PIMPI-studie bij prematuur en voldragen kinderen na DKT-vaccinatie tussen 20 en 24 weken zwangerschapsduur zijn steeds vergeleken met gegevens van een eerdere en vergelijkbare studie bij voldragen kinderen na DKT-vaccinatie tussen $30^{0/7}$-$33^{0/7}$w zwangerschapsduur (referentiecohort). Van deze laatste groep is uit epidemiologisch onderzoek gebleken dat de maternale DKT-vaccinatie de voldragen baby beschermt tegen ernstige kinkhoest in de eerste levensmaanden, totdat de baby zelf wordt gevaccineerd tegen kinkhoest.

In het eerste deel van dit proefschrift wordt ingegaan op DKT-specifieke antistofconcentraties in op tijd geboren en prematuur geboren kinderen na maternale DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur. Vervolgens is de reactogeniciteit en langere termijn veiligheid van een DKT-vaccinatie voor 24 weken zwangerschapsduur beschreven. Naast de PIMPI-studie is een pilotstudie beschreven die de overdracht van maternale antistoffen na DKT-vaccinatie van moeder naar kind beschrijft in het geval dat zwangere vrouwen met chronische inflammatoire aandoeningen zoals reuma medicatie gebruiken die de afweer onderdrukt. Voor lange termijn-veiligheid van maternale DKT-vaccinatie is daarnaast onderzoek op populatieniveau gedaan naar het vóórkomen van problemen als prematuriteit of overlijden van de vrucht in de periode voorafgaand aan de invoering van de maternale DKT-vaccinatie in het Rijksvaccinatieprogramma (eind 2019). Ook is de kinkhoestincidentie in het Caribische deel van Nederland onderzocht op basis van de hoogte van antistofconcentraties in het bloed, die sterk verhoogd zijn na een recente kinkhoestinfectie. Hiervoor is gebruik gemaakt van een zogenoemde serosurveillance-studie die werd uitgevoerd in Caribisch Nederland in 2017. Dit was van belang voor advisering over de invoering van maternale DKT-vaccinatie aldaar.

In het tweede deel van dit proefschrift worden andere aspecten van maternale vaccinatie verder uitgewerkt, zoals de sociaalpsychologische determinanten die van invloed zijn op de acceptatie van maternale DKT-vaccinatie door zwangere vrouwen, en het perspectief van verloskundig zorgverleners over de implementatie van de maternale DKT-vaccinatie als onderdeel van het Rijksvaccinatieprogramma.

Samenvatting van de hoofdstukken

Hoofdstuk 1 is de introductie van dit proefschrift en beschrijft de ziekte kinkhoest met de mogelijke klinische manifestaties, de geschiedenis en

epidemiologie van de ziekte, eerdere en huidige strategieën voor vaccinatie tegen kinkhoest, inclusief de maternale DKT-vaccinatie. Ook wordt de huidige surveillance van kinkhoest als onderdeel van het Rijksvaccinatieprogramma in Nederland beschreven.

Deel I

Hoofdstuk 2 beschrijft het design van de PIMPI-studie. De rationale voor de studie is gegeven samen met de doelstellingen, studieprocedures, inclusiecriteria, sample size berekeningen en gebruikte statistische onderzoeksmethoden.

Hoofdstuk 3 rapporteert antistofconcentraties in pasgeborenen na maternale DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur. De resultaten suggereren dat na een vroege DKT-vaccinatie rond 22 weken zwangerschapsduur, à terme (voldragen) kinderen op de leeftijd van twee maanden gemiddeld twee keer lagere maternale antistofconcentraties in het bloed hebben tegen pertussis toxine (anti-PT), in vergelijking met kinderen waarbij de moeder tussen $30^{0/7}$-$33^{0/7}$w zwangerschapsduur een DKT-vaccinatie heeft gekregen. Hogere concentraties van antistoffen tegen PT zijn geassocieerd met betere bescherming tegen het doormaken van kinkhoest, wat impliceert dat maternale DKT-vaccinatie voor 24 weken zwangerschapsduur mogelijk minder effectief is, en dat vaccinatie later in de zwangerschap de voorkeur heeft wat betreft voldragen kinderen. Na een premature geboorte werden op de leeftijd van twee maanden bijna vergelijkbare anti-PT concentraties gevonden als bij op tijd geboren kinderen in geval van DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur, naast licht verlaagde anti-filamentous hemagglutinine (anti-FHA) en anti-pertactine (anti-Prn) IgG-concentraties. In vergelijking met DKT-vaccinatie bij $30^{0/7}$-$33^{0/7}$w zwangerschapsduur bij voldragen kinderen, waren ook bij prematuren de antistofconcentraties twee tot drie keer lager op de leeftijd twee maanden. De klinische betekenis van deze bevindingen is onduidelijk omdat voor kinkhoest geen Correlate of Protection is gedefinieerd. Naast antistoffen spelen mogelijk ook andere factoren, al dan niet immunologisch, een rol in de bescherming tegen ernstige klinische kinkhoest in de eerste maanden na de geboorte. Om hier meer zicht op te krijgen, is het van belang om in geval van de diagnose kinkhoestinfectie bij zuigelingen ook gegevens op te vragen over het moment van maternale DKT-vaccinatie en het tijdsinterval tussen vaccinatie en geboorte.

Hoofdstuk 4 is een korte post-hoc analyse van de immunogeniciteitsstudie uit hoofdstuk 3 bij prematuren. Ondanks dat de sample size van de originele studie niet is berekend op het apart evalueren van vroeg- en laat-prematuren, suggereren de bevindingen dat vooral de antistofconcentraties van (extreem) vroege

prematuren (geboorte <$32^{0/7}$w zwangerschapsduur) duidelijk verlaagd zijn ten opzichte van op tijd geboren kinderen. De laat-prematuren (geboorte tussen $32^{0/7}$-$34^{6/7}$w zwangerschapsduur) hadden na maternale DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur antistofconcentraties die bijna op het niveau van voldragen kinderen zijn. Desalniettemin hadden voldragen en prematuur geboren kinderen na maternale DKT-vaccinatie voor 24 weken zwangerschapsduur nog steeds minimaal twee keer zo lage *B. pertussis*-specifieke antistofconcentraties ten opzichte van à terme kinderen na maternale DKT-vaccinatie tussen $30^{0/7}$-$33^{0/7}$w zwangerschapsduur (hoofdstuk 3). Ook de antistoffen tegen FHA en Prn zijn bij de geboorte bij vroeg-prematuren verlaagd. Behalve de lagere antistofconcentraties bij de geboorte, lijkt bij vroeg-prematuren ook de antistofdaling significant sneller (gemiddelde halfwaardetijd voor anti-PT 21.7 dagen) te verlopen dan in laat-prematuren en à terme kinderen (respectievelijk 32.9 en 32.2 dagen). Dit draagt bij aan de twee tot drie keer lagere antistoffen bij vroeg-prematuren op de leeftijd van twee maanden en pleit dus voor een vroege primaire vaccinatie tegen kinkhoest op de leeftijd van 6 weken, vooral in de groep van vroeg-prematuren.

Hoofdstuk 5 beschrijft een pilotstudie over de IgG-antistofrespons na maternale DKT-vaccinatie bij zwangere vrouwen met reumatische ziekten die medicatie gebruiken die de afweer onderdrukt. Terwijl de meeste medicatie de antistofrespons bij de moeder weinig beïnvloedt, werd bij bepaalde medicatie (biologicals, zoals Tumor Necrose Factor alpha-remmers (TNFis)) in navelstrengbloed een lagere anti-PT IgG antistofconcentratie gevonden in vergelijking met kinderen van moeders zonder TNFis of gezonde zwangere vrouwen na maternale DKT-vaccinatie. Het is beschreven dat TNFis (mild) de vaccinatierespons verminderen. Kinderen van moeders die tijdens de zwangerschap behandeld werden met TNFis zouden daarom beter tegen kinkhoest worden beschermd met een eerste vroege vaccinatie rond de leeftijd van 6 weken.

In **hoofdstuk 6** wordt de reactogeniciteit van maternale DKT-vaccinatie tussen $20^{0/7}$-$24^{0/7}$w zwangerschapsduur beschreven. De symptomen in de eerste week na vaccinatie bleken mild, en het merendeel van de symptomen duurde tussen 1 en 5 dagen. Slechts 0.6% van alle gevaccineerde vrouwen rapporteerden koorts (≥38.0˚C). Er werden geen verschillen gevonden in reactogeniciteit tussen maternale DKT-vaccinatie in het tweede of het derde trimester. Wat betreft negatieve zwangerschapsuitkomsten zoals vroeggeboorte of te laag geboortegewicht werden geen verhoogde risico's gevonden na DKT-vaccinatie tussen 20-24 weken in vergelijking met data van ongevaccineerde zwangeren uit 2018 op populatieniveau, want de maternale DKT-vaccinatie is opgenomen in het Rijksvaccinatieprogramma in 2019. Concluderend is ook tweede trimester

maternale DKT-vaccinatie veilig en wordt deze goed verdragen door zwangere vrouwen.

Hoofdstuk 7 gaat over achtergrondincidentie van negatieve zwangerschapsuitkomsten, onafhankelijk van maternale DKT-vaccinatie. De data werden verkregen uit de Nederlandse perinatale registratie, waarin uitgebreide data van meer dan 98% van alle zwangerschappen en bevallingen in Nederland zijn geregistreerd. Deze achtergronddata zijn belangrijk om zorgen over de veiligheid van maternale vaccinaties in perspectief te kunnen plaatsen en meldingen van mogelijke bijwerkingen van de maternale vaccinaties ná invoering maternale DKT-vaccinatie in Nederland (december 2019) te vergelijken met eerdere data zonder de maternale DKT-vaccinatie. Zoals altijd blijft reguliere monitoring van veiligheid en negatieve zwangerschapsuitkomsten belangrijk.

In **hoofdstuk 8** wordt de incidentie van *B. pertussis* infecties beschreven in het Caribische gebied van Nederland (CN), gebaseerd op een serosurveillance-studie die is uitgevoerd in 2017 op de Caribische eilanden. Ondanks het feit dat bijna geen klinische gevallen van kinkhoest waren gerapporteerd, werd op basis van antistofconcentraties tegen PT geschat dat ongeveer 8% van alle inwoners van 9 jaar en ouder een recente *B. pertussis* infectie had doorgemaakt in de twaalf maanden voor de bloedafname. Het hoogste percentage van recent geïnfecteerde personen werd gevonden in de leeftijdscategorie van 12-29 jaar, juist de leeftijdscategorie die kinderen krijgt. In het licht van de hoge incidentie van kinkhoest, in het bijzonder bij vrouwen in de vruchtbare leeftijdsgroep in CN, zou maternale DKT-vaccinatie daar een plaats moeten krijgen in het Rijksvaccinatieprogramma.

Deel II

Hoofdstuk 9 beschrijft sociaalpsychologische factoren die mogelijk de acceptatie van tweede trimester maternale DKT-vaccinatie kunnen voorspellen. De studie laat zien dat deze factoren niet verschillen van die van derde trimester vaccinatie. De factoren met de grootste invloed op het accepteren van maternale DKT-vaccinatie waren intentie en attitude ten opzichte van de vaccinatie, overtuigingen over (lange termijn) veiligheid en effectiviteit, risicoperceptie van (korte termijn) bijwerkingen van de vaccinatie en het voelen van een morele verantwoordelijkheid om het vaccin te nemen. Specifiek voor Nederland vonden vrouwen het prettig dat hun kind pas bij drie maanden de eerste DKTP-Hib-HepB vaccinatie kon krijgen in plaats van bij twee maanden en ook een vaccinatie minder (2+1 schema in plaats van 3+1 schema) nodig had, omdat de moeder al een maternale DKT-vaccinatie had gehad. Zorgpersoneel zou bovenstaande aspecten

vroeg tijdens de zwangerschap moeten bespreken met zwangere vrouwen, zodat deze een weloverwogen keuze kunnen maken of zij de maternale DKT-vaccinatie wel of niet nemen.

Volgens de resultaten van een studie die werd uitgevoerd als voorbereiding voor de studie uit hoofdstuk 10, en in het Nederlands is geschreven (**Appendix**), zijn de attitudes van verloskundig zorgverleners ten opzichte van maternale DKT-vaccinatie over het algemeen positief na het moment van implementatie van het vaccin in het Rijksvaccinatieprogramma. Gynaecologen waren vaker voorstander van het vaccineren tijdens de zwangerschap dan verloskundigen. De best mogelijke manier om bij zorgverleners kennis te verhogen over maternale DKT-vaccinatie en preventie van kinkhoest bij pasgeborenen, is het bieden van (online) trainingen vóór de implementatie van maternale vaccinatiestrategieën als onderdeel van het Rijksvaccinatieprogramma. Daarnaast moet blijvend informatie beschikbaar worden gesteld over de veiligheid en effectiviteit van de vaccinatie.

Hoofdstuk 10 rapporteert ook over het perspectief van verloskundig zorgverleners aangaande maternale DKT-vaccinatie, maar op een kwalitatieve manier. De interviews die waren gevoerd met verloskundig zorgverleners suggereren dat de implementatie van een nieuwe vaccinatie, in een nieuwe doelgroep, en uitgevoerd door een nieuwe groep verloskundig zorgverleners, duidelijkheid en transparantie vereist over wat er van hen gevraagd wordt voorafgaand aan de invoering in het programma. In het geval van maternale DKT-vaccinatie vragen zorgverleners om duidelijke en uitgebreide voorlichting over de vaccinatiestrategie, de acties die van hen worden verwacht en wanneer die moeten worden uitgevoerd. De resultaten van de studie benadrukken hoe belangrijk het is om de relevante zorgprofessionals vroegtijdig te betrekken bij de implementatie van een nieuwe vaccinatiestrategie. Er moet rekening gehouden worden met mogelijke barrières die de zorgverleners ervaren in het implementatietraject. Zo kunnen zorgverleners beter worden geïnformeerd over de voordelen en veiligheid van maternale vaccinatie. Uiteindelijk zal dat de vaccinatiegraad ten goede komen, aangezien zwangere vrouwen vaak het meest vertrouwen op de informatie die zij krijgen van hun zorgverlener.

Samenvattend beschrijft dit proefschrift verschillende aspecten van tweede trimester ten opzichte van derde trimester maternale DKT-vaccinatie. Vaccinatie voor 24 weken zwangerschapsduur blijkt suboptimaal voor transplacentaire antistofoverdracht en kan mogelijk de bescherming tegen kinkhoest verminderen. Bij laat-prematuren, geboren na 32 weken zwangerschapsduur, leidde maternale DKT-vaccinatie voor 24 weken zwangerschapsduur tot vrijwel vergelijkbare antistofconcentraties tegen PT als in op tijd geboren kinderen na DKT-vaccinatie

voor 24 weken zwangerschapsduur, maar wel twee keer lager dan na DKT-vaccinatie tussen de 30 en 33 weken zwangerschapsduur. Bij vroeg-prematuren geboren voor 32 weken waren de beschermende antistofconcentraties bij de geboorte al lager, en namen bovendien na de geboorte sneller af. Het is op dit moment nog onbekend welke antistofconcentraties geassocieerd zijn met bescherming tegen kinkhoest bij pasgeborenen. Zolang er geen 'Correlate of Protection' beschikbaar is, is het moeilijk te bepalen wat de 'window of opportunity' is tijdens de zwangerschap voor maternale DKT-vaccinatie voor het optimaal beschermen van op tijd geboren kinderen tegen kinkhoest, maar zeker voor prematuren. Behalve de hoogte van de antistoffen bij de geboorte is de halfwaardetijd en de kwaliteit van de antistoffen (zoals antistofaffiniteit) belangrijk. De overdracht van cellulaire immuniteit na maternale vaccinatie is een ander relevant aspect, maar nog onderbelicht.

Met een groeiend aantal maternale vaccinaties tegen verschillende verwekkers in de nabije toekomst, en de onzekerheid wat meerdere vaccinaties tijdens een zwangerschap doen met de acceptatie door zwangere vrouwen, blijft het belangrijk om de zowel immunologische factoren en de impact op de immuunrespons bij kinderen na maternale vaccinatie te monitoren, naast de effectiviteit, maar ook de acceptatie en vaccinatiegraad. Onderzoek naar bovengenoemde en andere kennishiaten blijft nodig voor het verder ontwikkelen en optimaliseren van vaccinatiestrategieën. Voor kinkhoest is dit extra belangrijk, omdat er sinds de winter van 2023-2024 in Nederland een nieuwe ernstige verheffing van kinkhoest is gezien met opnieuw sterfte van zuigelingen aan kinkhoest. Kinkhoest zal endemisch blijven totdat betere vaccins zijn ontwikkeld en een optimale vaccinatiegraad wordt bereikt.

Appendices

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Appendices

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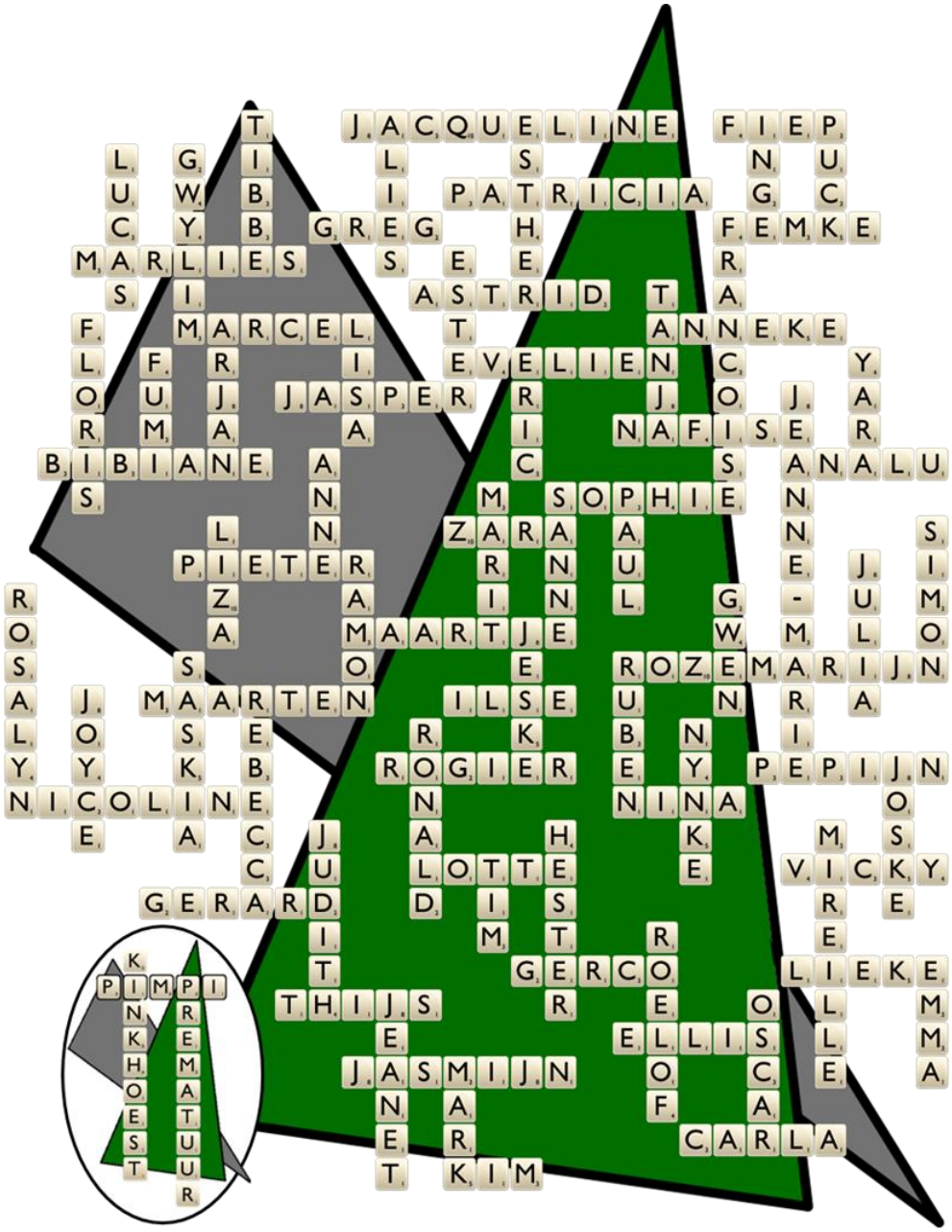

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Appendices

About the author

Maarten Maurits Immink was born on the 4th of February, 1993 in Utrecht, the Netherlands. He grew up as the middle child in a loving family with his parents Marcel and Saskia, his older brother Jasper and younger sister Femke. After graduating from secondary school at the Oosterlicht College in Nieuwegein in 2010, he studied Life Sciences at HU university in Utrecht, which he finished in 2015 with a major in medical microbiology. Following his bachelor, he obtained his MSc degree in clinical epidemiology in 2018 by finishing the master Evidence Based Practice in Healthcare at the University of Amsterdam. During an internship at the UMC Utrecht - Julius Center for Health Sciences and Primary Care, he completed his master thesis entitled '*Long-Term Mortality in Patients with Community-Acquired Pneumonia Following Empirical Antibiotic Treatment Strategies*'.

Directly after graduating from his master, he applied for a job as a PhD candidate at the National Institute for Public Health and the Environment (RIVM), at the Center for Infectious Disease Control, under supervision of Prof. dr. Elisabeth Sanders, Prof. dr. Mireille Bekker and Dr. Nicoline van der Maas. In collaboration with the UMC Utrecht, he conducted a clinical trial investigating three major aspects of maternal immunization against pertussis, i.e. immunogenicity, reactogenicity and acceptance of vaccination in the second versus the third trimester of pregnancy, with particular focus on the benefits for preterm infants. After finishing his PhD project, he worked at Perined (the institute that is responsible for the Dutch perinatal registry) for a short time.

During his PhD project, he developed a great interest in the field of medicine. In September 2023, he started studying medicine at Utrecht University.

Appendices

List of publications

Immink MM, Bekker MN, de Melker HE, Rots NY, Sanders EAM, van der Maas NAT. Study protocol of the PIMPI-project, a cohort study on acceptance, tolerability and immunogenicity of second trimester maternal pertussis immunization in relation to term and preterm infants. BMC Infect Dis. 2021 Sep 3;21(1):897.

Immink MM, Bekker MN, de Melker HE, den Hartog G, Rots NY, van Gageldonk PGM, Groenendaal F, Sanders EAM, van der Maas NAT. Maternal Pertussis Immunization and Immunoglobulin G Levels in Early- to Late-Term and Preterm Infants. JAMA Netw Open. 2024 Jul 1;7(7):e2424608.

Immink MM, van der Maas NAT, Bekker MN, de Melker HE, den Hartog G, Rots NY, van Gageldonk PGM, Groenendaal F, Sanders EAM. Decay rates of maternal tetanus, diphtheria and pertussis antibody levels in early- and moderate-to-late preterm and term infants at birth and at 2 months. Accepted for publication in Open Forum Infectious Diseases. 2024.

Immink MM, Ghalandari N, Röder E, Bruijning-Verhagen PCJ, Smeele H, Crijns H, van der Maas NAT, Bekker MN, Sanders EAM, Dolhain RJEM. Maternal and neonatal antibody levels on pertussis vaccination in pregnant women on immune-modulating therapy for rheumatic disease. RMD Open. 2023 Aug;9(3):e002985.

Immink MM, Kemmeren JM, Broeders L, Bekker MN, de Melker HE, Sanders EAM, van der Maas NAT. Reactogenicity and safety of second trimester maternal tetanus, diphtheria and acellular pertussis vaccination in the Netherlands. Vaccine. 2023 Jan 27;41(5):1074-1080.

Immink MM, Koole S, Bekker MN, Groenendaal F, Kemmeren JM, de Melker HE, van der Maas NAT. Background incidence rates of adverse pregnancy outcomes in the Netherlands: Data of 2006-2018. Eur J Obstet Gynecol Reprod Biol. 2021 Jan;256:274-280.

Immink MM, Vos ERA, Janga-Jansen AVA, Baboe-Kalpoe S, Hulshof K, van Vliet J, Kerkhof J, den Hartog G, de Melker HE, van der Klis FRM, van der Maas NAT. Circulation of *Bordetella pertussis* in the Caribbean Netherlands: a population-based seroepidemiological study. Int J Infect Dis. 2021 Oct;111:21-27.

Immink MM, van der Maas NAT, de Melker HE, Ferreira JA, Bekker MN. Socio-psychological determinants of second trimester maternal pertussis vaccination acceptance in the Netherlands. Vaccine. 2023 May 22;41(22):3446-3453.

Immink MM, Pluijmaekers AJM, Bekker MN, de Melker HE, van der Maas NAT, van Zoonen K. Maternale vaccinatie tegen kinkhoest in het Rijksvaccinatieprogramma: evaluatie onder verloskundig zorgverleners 1 jaar na de implementatie in december 2019. Infectieziekten Bulletin. 2022 Jan 01.

Immink MM, van Zoonen K, Jager NM, Pluijmaekers AJM, de Melker HE, van der Maas NAT, Bekker MN. Maternal vaccination against pertussis as part of the national immunization program: a qualitative evaluation among obstetric care providers one year after the implementation in December 2019. BMC Health Serv Res. 2023 Mar 30;23(1):311.