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Immunogenicity, transplacental transfer of pertussis antibodies and safety following pertussis immunization during pregnancy: Evidence from a randomized, placebo-controlled trial

Kirsten P. Perrett [a], Scott A. Halperin [b], Terry Nolan [a], Cristina Martínez Pancorbo [c], Bruce Tapiero [d], Federico Martinón-Torres [e], Zbynek Stranak [f], Miia Virta [g], Otto G. Vanderkooi [h], Pavel Kosina [i], Maria Begoña Encinas Pardilla [j], Ignacio Cristobal García [k], Gian Vincenzo Zuccotti [l], Lusine Kostanyan [m], Nadia Meyer [n], Maria Angeles Ceregido [n], Brigitte Cheuvart [n], Sherine O. Kuriyakose [o], Manuel Marcos Fernández [p], Miguel Ángel Rodríguez Zambrano [q], Adrián Martín García [r], Juan Eloy Asenjo de la Fuente [s], Maria Dolores Camacho Marín [s], María de la Calle Fernández-Miranda [t], Yolanda Romero Espinar [u], Paola Giovanna Marchisio [v], Paolo Manzoni [w], Narcisa Mesaros [n,*]

[a] Murdoch Children's Research Institute and Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia
[b] Dalhousie University, Canadian Center for Vaccinology, Halifax, Canada
[c] Instituto Sevillano de la Mujer-Instituto Hispalense de Pediatría, Seville, Spain
[d] CHU Sainte Justine, Université de Montréal, Montréal, Canada
[e] Translational Pediatrics and Infectious Diseases, Pediatrics Department, Hospital Clínico Universitario de Santiago de Compostela and Genetics, Vaccines and Pediatrics Research Group, University of Santiago de Compostela, Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago de Compostela, Spain
[f] Institute for the Care of Mother and Child, Prague, Czech Republic
[g] Tampere Vaccine Research Center, Tampere University, Tampere, Finland
[h] Alberta Children's Hospital, University of Calgary, Alberta, Calgary, Canada
[i] University Hospital, Hradec Kralove, Czech Republic
[j] Hospital Universitario Puerta de Hierro, Majadahonda, Spain
[k] Universidad Francisco de Vitoria, Madrid, Spain
[l] Ospedale dei Bambini Vittore Buzzi and University of Milan, Milan, Italy
[m] Modis, C/O GSK, Wavre, Belgium
[n] GSK, Wavre, Belgium
[o] GSK, Bangalore, India
[p] Hospital Monteprincipe, Boadilla del Monte, Spain
[q] Hospital HM Puerta del Sur, Móstoles, Spain
[r] Nuevo Hospital Universitario de Burgos, Burgos, Spain
[s] Hospital Clínico San Carlos, Madrid, Spain
[t] Hospital La Paz, Madrid, Spain
[u] Hospital Quirónsalud Málaga, Málaga, Spain
[v] Università degli Studi di Milano, Milan, Italy
[w] Ospedale Ostetrico Ginecologico Sant'Anna, Turin, Italy and Department of Maternal-Infant-Pediatric Health, Degli Infermi Hospital, Biella, Italy

Abbreviations: AE, adverse event; ATP, according-to-protocol; CI, confidence interval; ELISA, enzyme-linked immunosorbent assays; FHA, filamentous hemagglutinin; GMC, geometric mean concentration; ICF, informed consent form; LL, lower limit; LLoQ, lower limit of quantitation; PRN, pertactin; PT, pertussis toxoid; SAE, serious adverse event; Tdap, diphtheria-tetanus-acellular pertussis vaccine; TVC, total vaccinated cohort; UK, United Kingdom; US, United States.

* Corresponding author at: GSK, Avenue Fleming 20, 1300 Wavre, Belgium.
E-mail addresses: kirsten.perrett@rch.org.au (K.P. Perrett), scott.halperin@dal.ca (S.A. Halperin), t.nolan@unimelb.edu.au (T. Nolan), b.tapiero@umontreal.ca (B. Tapiero), federico.martinon.torres@sergas.es (F. Martinón-Torres), z.stranak@seznam.cz (Z. Stranak), miia.virta@staff.uta.fi (M. Virta), ovanderk@ucalgary.ca (O.G. Vanderkooi), kosinpav@seznam.cz (P. Kosina), icristobalg@sego.es (I. Cristobal García), gianvincenzo.zuccotti@unimi.it (G.V. Zuccotti), lusine.x.kostanyan@gsk.com (L. Kostanyan), nadia.x.meyer@gsk.com (N. Meyer), maria-angeles.x.ceregido@gsk.com (M.A. Ceregido), brigitte.cheuvart@gsk.com (B. Cheuvart), sherine.o.kuriyakose@gsk.com (S.O. Kuriyakose), mmarcos@egom.es (M. Marcos Fernández), eloyasenjo@telefonica.net (J.E. Asenjo de la Fuente), paola.marchisio@unimi.it (P.G. Marchisio), narcisa.x.mesaros@gsk.com (N. Mesaros).

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ABSTRACT

Background: Pertussis immunization during pregnancy is recommended in many countries. Data from large randomized controlled trials are needed to assess the immunogenicity, reactogenicity and safety of this approach.

Methods: This phase IV, observer-blind, randomized, placebo-controlled, multicenter trial assessed immunogenicity, transplacental transfer of maternal pertussis antibodies, reactogenicity and safety of a reduced-antigen-content diphtheria-tetanus-three-component acellular pertussis vaccine (Tdap) during pregnancy. Women received Tdap or placebo at 27–36 weeks' gestation with crossover ≤ 72-hour-postpartum immunization. Immune responses were assessed before the pregnancy dose and 1 month after, and from the umbilical cord at delivery. Superiority (primary objective) was reached if the lower limits of the 95% confidence intervals (CIs) of the pertussis geometric mean concentration (GMC) ratios (Tdap/control) in cord blood were ≥ 1.5. Solicited and unsolicited adverse events (AEs) and pregnancy-/neonate-related AEs of interest were recorded.

Results: 687 pregnant women were vaccinated (Tdap: N = 341 control: N = 346). Superiority of the pertussis immune response (maternally transferred pertussis antibodies in cord blood) was demonstrated by the GMC ratios (Tdap/control): 16.1 (95% CI: 13.5–19.2) for anti-filamentous hemagglutinin, 20.7 (15.9–26.9) for anti-pertactin and 8.5 (7.0–10.2) for anti-pertussis toxoid. Rates of pregnancy-/neonate-related AEs of interest, solicited general and unsolicited AEs were similar between groups. None of the serious AEs reported throughout the study were considered related to maternal Tdap vaccination.

Conclusions: Tdap vaccination during pregnancy resulted in high levels of pertussis antibodies in cord blood, was well tolerated and had an acceptable safety profile. This supports the recommendation of Tdap vaccination during pregnancy to prevent early-infant pertussis disease.

Clinical Trial Registration. ClinicalTrials.gov: NCT02377349.

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1. Introduction

Pertussis (*Bordetella pertussis*), a highly contagious acute respiratory tract infection, remains a particular and potentially life-threatening burden for infants too young to be vaccinated [1,2]. To combat a sustained increase in pertussis disease morbidity and mortality in infants in the United States (US), United Kingdom (UK), Australia and other countries from 2008 to 2012 [2], innovative strategies to complement the widespread national childhood immunization programs were urgently pursued. Cocooning, a strategy of indirect protection where postpartum mothers and others in close contact with infants are vaccinated, was implemented as an emergency measure in several countries [2–4]. An alternate strategy of direct protection via neonatal immunization has also shown promise in some clinical trials [5–7]. However, because of the difficulty in successfully implementing complex cocoon strategies [8,9] and the existence of a neonatal susceptibility gap before a sufficient immune response is achieved with the birth-dose approach [7], maternal immunization has become the most commonly implemented strategy [4].

Immunization during pregnancy provides passive protection to the newborn via transfer of maternal antibodies through the placenta and indirect protection by preventing pertussis in the mother [10,11]. In 2011, the US became the first country to recommend pregnant women to be vaccinated with a pertussis-containing vaccine [12]. The following year, the UK introduced a temporary emergency maternal pertussis immunization program [13]. These pivotal maternal immunization recommendations were implemented with limited direct evidence of the efficacy or safety of this approach [10].

In this randomized placebo-controlled trial, we examined the immunogenicity of a reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine (Tdap) administered during the third trimester of pregnancy, the transplacental transfer of maternal pertussis antibodies and the safety of Tdap vaccination for the mother, fetus and neonate.

2. Methods

2.1. Study design and participants

This phase IV, multi-center, observer-blind, randomized, placebo-controlled, crossover trial was conducted between 14 October 2015 and 24 October 2017 in Australia, Canada, Czech Republic, Finland, Italy and Spain. The trial (ClinicalTrials.gov: NCT02377349) was conducted according to the principles of Good Clinical Practice, the Declaration of Helsinki and applicable regulations. The centers' Institutional Review Boards and/or Ethics Committees (Supplementary material) approved the protocol and informed consent form. An independent data monitoring committee oversaw the participants' and their fetuses'/newborns' safety.

We enrolled healthy women 18–45 years old, at $27^{0/7}$–$36^{6/7}$ weeks' gestation (as established by ultrasound examination), who were not at known risk of pregnancy-related complications and had a normal singleton pregnancy. Exclusion criteria included previous vaccination with diphtheria (toxoid), tetanus (toxoid) or pertussis antigens during the current pregnancy; history of physician-diagnosed or laboratory-confirmed pertussis within the past 5 years; chronic administration of immune-modifying drugs; immunosuppressive or other serious underlying medical conditions; and immunization within 30 days before/after study vaccine administration (except seasonal influenza vaccine). Detailed inclusion and exclusion criteria are provided in the Supplementary methods. Each participant provided written informed consent before enrollment.

2.2. Randomization and blinding

We randomized women (1:1) to a Tdap group and a control (placebo) group. Allocation of participants was performed at the study centers using a central internet-based randomization system. The randomization algorithm used center, age (18–24 years, 25–34 years, 35–45 years), gestational age at vaccination (27–

32 weeks, 33–36 weeks) and country as minimization factors, each having an equal weight in the algorithm.

Data were collected in an observer-blind manner: the participants and study personnel responsible for evaluating the study endpoints and for laboratory testing were unaware of the vaccine given. Vaccines were prepared and administered by study personnel not involved in the analyses.

2.3. Procedures

Women in the Tdap group received a single reduced-antigen-content Tdap dose at 27–36 weeks' gestation (visit 1) and a placebo dose ≤ 72 h post-delivery (visit 3); women in the control group received the reverse—placebo at 27–36 weeks' gestation and Tdap post-delivery (Fig. 1). Each Tdap dose (*Boostrix*, GSK) contained ≥ 2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 μg pertussis toxoid (PT), 8 μg filamentous hemagglutinin (FHA), 2.5 μg pertactin (PRN) and 500 μg Al^{3+}. Each placebo dose contained 150 mM NaCl. Both were injected intramuscularly in the deltoid muscle of the non-dominant arm. Eight different commercial lots of Tdap vaccine were used (Supplementary material).

Blood samples were collected from all women before and 1 month (allowed interval: 21–48 days) after the pregnancy dose (~5 mL) and from the umbilical cord at delivery (~2.5 mL) (Fig. 1). Antibodies to the Tdap antigens were quantified at GSK, Rixensart/Wavre, Belgium using validated enzyme-linked immunosorbent assays (ELISAs). Assay cut-offs (lower limits of quantitation) were 0.057 IU/mL (anti-diphtheria), 0.043 IU/mL (anti-tetanus), 2.046 IU/ml (anti-FHA), 2.187 IU/ml (anti-PRN) and 2.693 IU/mL (anti-PT). Seroprotection against diphtheria and tetanus was defined as an antibody concentration ≥ 0.1 IU/mL [14,15]. No correlate of protection has been established for pertussis [16].

At each vaccination visit (visits 1 and 3, Fig. 1), participants received diary cards to record solicited local (injection site pain, redness, swelling) and general (fever, headache, fatigue, gastrointestinal symptoms) adverse events (AEs) within 8 days and unsolicited AEs within 31 days post-vaccination. All pregnancy- and neonate-related AEs of interest (defined and graded as described by Munoz et al [17]: gestational diabetes, pregnancy-related hypertension, premature rupture of membranes, preterm premature rupture of membranes, premature labor, premature uterine contractions, intrauterine growth restriction/poor fetal growth, pre-eclampsia, eclampsia, vaginal or intrauterine hemorrhage, maternal death, preterm birth, neonatal death, small for gestational age, neonatal hypoxic-ischemic encephalopathy, and failure to thrive/growth deficiency) had to be recorded on the diary cards from receipt of the first vaccine or placebo dose until study end (visit 4, 2 months after delivery). All adverse pregnancy outcomes (live birth with/without congenital anomalies, still birth with/without congenital anomalies, elective termination with/without congenital anomalies) and pregnancy- and neonate-related AEs of interest were reported as serious adverse events (SAEs). Other SAEs were also recorded from the first vaccine or placebo dose until study end. If participants noticed any large injection site reactions (any local swelling with diameter > 100 mm, any noticeable diffuse injection site swelling or any noticeable increased circumference of the injected limb), they had to contact the study personnel and visit the investigator's office for evaluation as soon as possible. Diary cards were collected and verified during a discussion between the investigator and the participant on visits 2, 3 and 4. Any unreturned diary cards were sought from the participants through phone calls or any other convenient procedure. The investigators assessed the intensity of all AEs and their causal relation to vaccination. All information relevant to the (S)AEs were recorded on an electronic case report form.

2.4. Objectives

The primary objective was to demonstrate that the amount of maternally transferred pertussis antibodies in cord blood of Tdap-vaccinated mothers was superior to that in cord blood of placebo-vaccinated mothers in terms of geometric mean concentrations (GMCs) for pertussis antibodies. Superiority was reached if the lower limits (LLs) of the 95% confidence intervals (CIs) of the GMC ratios (Tdap divided by control) for anti-FHA, anti-PRN and anti-PT antibodies were ≥ 1.5.

Secondary immunogenicity objectives encompassed assessing pertussis seropositivity rates in cord blood samples; and Tdap immunogenicity in pregnant women in terms of seroprotection/seropositivity rates, vaccine response (only shown here for pertussis) and antibody GMCs 1 month post-vaccination.

Secondary safety objectives included assessing pregnancy outcomes and pregnancy-/neonate-related AEs of interest until study end (2 months after delivery); occurrence of solicited local and

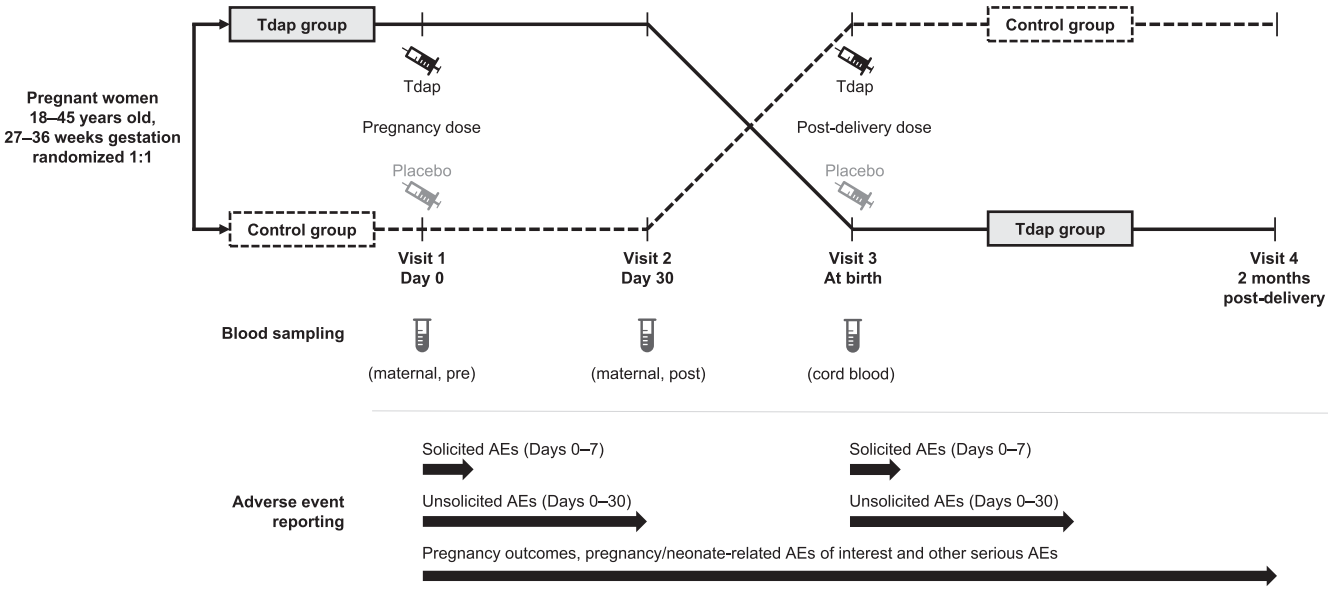

Fig. 1. Study design. Abbreviations: AE, adverse event; Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.

general AEs within 8 days and unsolicited AEs within 31 days after the pregnancy and post-delivery doses; and SAEs in the mothers and their infants throughout the study (Fig. 1).

2.5. Statistical analyses

The target sample size was 680 participants (340 per group). Assuming a drop-out rate of 20%, this would result in 272 evaluable participants per group, which would provide > 96% overall power to reach the primary objective.

The primary immunogenicity analyses were based on the according-to-protocol (ATP) cohort for immunogenicity, including all eligible participants who received the study vaccines per protocol, complied with study procedures and intervals, had the cord blood collection at least 21 days post-vaccination and had immunogenicity results available for at least one Tdap antigen. For the primary superiority objective, the 95% CIs of the GMC ratios were computed using a two-sample *t* test assuming heterogeneity of variance. Seroprotection/seropositivity and vaccine response rates were calculated with exact 95% CIs. GMCs were calculated with 95% CIs. The definition of vaccine response for pertussis is included in the results section (table footnote). We also performed immunogenicity subgroup analyses by gestational age at the pregnancy dose.

The primary analyses for safety were based on the total vaccinated cohort (TVC), including all participants with documented vaccination. Percentages of participants reporting solicited or unsolicited AEs were calculated with exact 95% CIs. SAEs were described in detail.

All endpoint analyses, except for the primary endpoints, were descriptive. Statistical analyses were performed using SAS version 9.2.

3. Results

3.1. Study population

725 pregnant women were enrolled, 690 were randomized, 687 (Tdap: N = 341; control: N = 346) were included in the TVC and 660 completed the study (96% of those randomized). The ATP cohort for immunogenicity comprised 583 participants (Tdap: N = 291; control: N = 292; 84% of those randomized) (Fig. 2). Baseline characteristics were comparable between groups (Table 1). In the TVC, the mean gestational age at the pregnancy dose was 31.8 weeks (Tdap) and 31.6 weeks (control). The mean time between vaccination and delivery was 50.6 (Tdap) and 52.4 days (control) (Table 1).

3.2. Immunogenicity

The primary objective of the study was met: the amount of maternally transferred pertussis antibodies in cord blood of Tdap-vaccinated mothers was superior to that in cord blood of control mothers because the LLs of the 95% CIs of the anti-FHA, anti-PRN and anti-PT GMC ratios (Tdap/control) were $\geq$ 1.5 (Table 2). GMCs for maternally transferred pertussis antibodies in cord blood were 8.5–20.7-fold higher for Tdap-vaccinated than for control mothers.

Similarly, anti-FHA, anti-PRN and anti-PT antibody GMCs in Tdap-vaccinated pregnant women were 11.1–27.0-fold higher than in controls 1 month after the pregnancy dose (Table 3). Post-vaccination antibody GMCs and seropositivity rates in pregnant women were similar to those in cord blood samples for the respective groups (with a > 1 ratio of cord blood to maternal antibody GMCs) (Tables 2 and 3). One month after the pregnancy dose, 93.4%, 89.6% and 87.8% of women in the Tdap group mounted a vaccine response against FHA, PRN and PT, respectively, compared to $\leq$ 1.4% in the control group (Table 3).

When analyzing the pertussis immune response by gestational age at the pregnancy dose, higher anti-PRN antibody GMCs were observed in infant cord blood from mothers vaccinated at 27–32 weeks' compared to 33–36 weeks' gestation (Table 4).

One month after the pregnancy dose, 97.6% and 100% of women in the Tdap group were seroprotected against diphtheria and tetanus, respectively, compared to 70.6% and 96.6% in the control group (Table 5). Anti-diphtheria and anti-tetanus antibody GMCs increased after Tdap vaccination and were 8.6–9.5-fold higher in the Tdap than in the control group (Table 5).

3.3. Reactogenicity and safety

Compliance in returning diary cards in the Tdap group was 98.2% after the pregnancy dose and 96.4% after the post-delivery dose (for solicited and unsolicited AEs); in the control group, compliance was 98.8% and 99.1% after the pregnancy dose and 96.8% and 96.5% after the post-delivery dose (for solicited and unsolicited AEs, respectively).

341 pregnancies in the Tdap and 345 in the control group resulted in live births; congenital anomalies were reported for 9 infants (2.6%) in the Tdap and 8 (2.3%) in the control group (Table 6 and Supplementary Table 1). One woman in the control group was lost to follow-up before delivery.

Pregnancy-/neonate-related AEs of interest were reported at similar rates in both groups, the most common being premature labor (Tdap: 3.8%; control: 3.2%) and premature rupture of membranes (Tdap: 3.8%; control: 4.3%) (Table 6). Eleven infants (3.2%) in the Tdap group and nine (2.6%) in the control group were born prematurely. There were no maternal or neonatal deaths. At birth, the infants' mean gestational age, weight and Apgar scores were comparable between groups (Tables 1 and 6).

Pain was the most commonly reported solicited local AE after the pregnancy and post-delivery doses (Table 7). Solicited general AEs were reported at similar rates in both groups after the pregnancy dose and after the post-delivery dose (Table 7). Solicited AEs were mostly mild or moderate (Table 7). There were no reports of large injection site reactions within 8 days after either dose. The incidence of unsolicited AEs was similar in both groups after the pregnancy and post-delivery doses, for the mothers (Table 7) and their infants (Supplementary table 2).

Between the pregnancy and post-delivery doses, 45 women (13.2%) in the Tdap group reported 56 SAEs and 48 women (13.9%) in the control group reported 64 SAEs (Supplementary table 3). One of these SAEs (premature labor in a woman in the control group) was assessed as related to (placebo) vaccination. There were two cases of chorioamnionitis in the control and none in the Tdap group. Between the post-delivery dose and study end, eight women (2.4%) in the Tdap group reported eight SAEs and five women (1.5%) in the control group reported six SAEs (Supplementary table 4).

77 SAEs were reported for 52 infants (15.2%) in the Tdap group and 63 SAEs for 45 infants (13.0%) in the control group (Supplementary table 1). None of the SAEs in infants were assessed as maternal Tdap vaccination-related; one (respiratory distress in an infant in the Tdap group, Fig. 2) led to a withdrawal.

Supplementary Fig. 1 summarizes these findings and highlights their clinical relevance.

4. Discussion

Maternal pertussis immunization has undergone a paradigm shift in recent years as evidence emerges of robust effectiveness

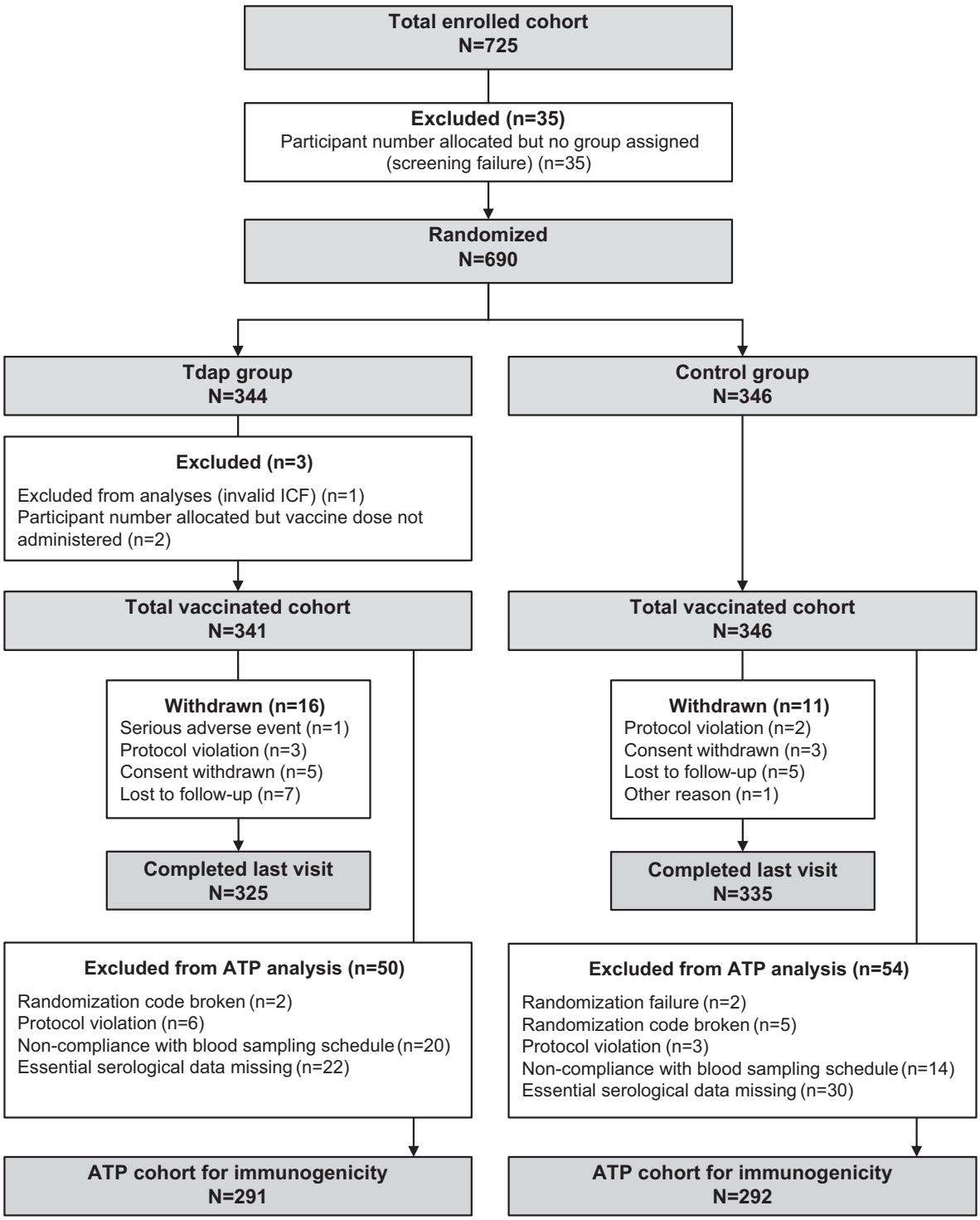

Fig. 2. Participant flow diagram. Abbreviations: ATP, according-to-protocol; ICF, informed consent form; N, number of participants per cohort/group; n, number of participants with the specified elimination code assigned (excluding those for whom a lower elimination code number was assigned); Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.

and safety in protecting young infants and their mothers against pertussis [18–21]. However, performing clinical trials in pregnant women is challenging [22], hence the vast majority of immunogenicity and safety data has come from observational studies, which are prone to bias [23]. To our knowledge, only five randomized controlled trials (two placebo-controlled) have directly assessed the immunogenicity and safety of pertussis vaccination during pregnancy [24–28]. The increasing number of countries recommending maternal Tdap vaccination reduces the likelihood that additional randomized placebo-controlled trials will be performed. With 687 vaccinated pregnant women from six countries, our trial is currently the largest placebo-controlled randomized trial on maternal pertussis immunization and one of two randomized controlled trials to assess the three-component pertussis Tdap vaccine administered during pregnancy [28]. Our trial has shown that Tdap immunization during the third trimester of pregnancy was well

Table 1
Characteristics of participants in the total vaccinated cohort.

	Tdap group (N = 341)	Control group (N = 346)
Mean age ± SD at pregnancy dose, years	32.7 ± 4.4	32.5 ± 4.3
Age category at pregnancy dose, n (%)		
18–24 years	10 (2.9)	13 (3.8)
25–34 years	214 (62.8)	215 (62.1)
35–45 years	117 (34.3)	118 (34.1)
Ethnic origin, n (%)		
White[a]	317 (93.0)	326 (94.2)
Asian	9 (2.6)	2 (0.6)
Other	15 (4.4)	18 (5.2)
Mean BMI ± SD, kg/m^2	27.5 ± 4.4	28.2 ± 5.1
Mean gestational age at pregnancy dose ± SD, weeks	31.8 ± 2.7	31.6 ± 2.7
Gestational age category at pregnancy dose, n (%)		
<27 weeks	0 (0.0)	1 (0.3)[b]
27–32 weeks	204 (59.8)	200 (57.8)
33–36 weeks	136 (39.9)	145 (41.9)
>36 weeks	1 (0.3)	0 (0.0)
Mean gestational age at delivery ± SD, weeks	39.1 ± 1.3	39.3 ± 1.2
Mean time between pregnancy dose and delivery ± SD, days	50.6 ± 20.4	52.4 ± 19.7
Breastfeeding, n (%)		
Never	12 (3.7)	23 (6.9)
No	27 (8.4)	34 (10.1)
Yes	284 (87.9)	278 (83.0)
Missing	18	11

Abbreviations: ATP, according-to-protocol; BMI, body mass index; N, total number of participants per group and cohort; n (%), number (percentage) of participants in the specified category; SD, standard deviation; Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.

[a] Includes White – Caucasian/European heritage (majority) and White – Arabic/North African heritage (3 in Tdap and 7 in control group).

[b] This participant was considered < 27 weeks of gestation at the pregnancy dose for analysis, however after database freeze it was confirmed by the investigator that the gestational age for this participant at the pregnancy dose was 27 weeks.

tolerated, did not increase the risk of pregnancy-/neonate-related AEs of interest or abnormal pregnancy outcomes, elicited strong antibody responses in women and provided high levels of pertussis antibodies to the newborn infant.

The primary objective of the study was achieved; the amount of maternally transferred pertussis antibodies in cord blood of Tdap-vaccinated mothers was superior to that in cord blood of placebo-vaccinated mothers, with 8.5–20.7-fold higher GMCs in cord blood of Tdap- vs placebo-vaccinated mothers. This finding is consistent with other randomized controlled trials [24–28] and observational (prospective or retrospective cohort) studies [29–32] that compared pertussis antibody levels in cord blood of pertussis-vaccinated mothers to cord blood of control (placebo, Td, TT or unvaccinated) mothers. GMC ratios (Tdap/control) for pertussis antibodies ranged from 2.7 to 22.2 (vs 8.5 in our study) for PT, 3.4 to 21.2 (vs 16.1 in our study) for FHA and 5.5 to 44.0 (vs 20.7 in our study) for PRN [24–30,32].

The immunogenicity of Tdap vaccination in pregnant women in our study was analogous to that found in previous studies, with consistently higher pertussis antibody concentrations after Tdap vaccination than after control or no vaccination [24,26,30]. Although direct comparisons between studies for immunogenicity are inherently difficult due to different laboratories and assays used, timing of vaccination during pregnancy, study design and other factors (e.g., epidemiological background of the study population), these findings are reassuring. In addition, our finding of a > 1 ratio of cord blood to maternal antibody (1 month post-vaccination) for FHA, PT and PRN in Tdap-recipient infant-maternal pairs and placebo-recipient pairs demonstrated an active transport of pertussis antibodies across the placenta.

The optimal timing of maternal pertussis immunization for antibody transfer to the fetus is a critical issue. The initial recommendation in the US was vaccination between 27 and 36 weeks' gestation while the UK elected to recommend a narrower window between 28 and 32 weeks' gestation (but allowing vaccination up to 38 weeks) [12,13]. Recent observational studies have suggested that higher anti-pertussis antibody concentrations may be achieved in cord blood when mothers are vaccinated earlier: 27–30 weeks' gestation compared to later [29], 28–32 weeks' compared to 33–36 weeks' gestation [33], or second- vs third-trimester immunization [34]. Current recommendations vary by country, e.g., UK: 16–32 weeks' [35], Canada: 27–32 weeks' [36], US: 27–36 weeks' [12] and Australia: 20–32 weeks' gestation [37]. In our trial, we found higher PRN GMCs in cord blood of mothers vaccinated at 27–32 vs 33–36 weeks' gestation. However, as our trial was not powered for this outcome, this observation may also be due to confounding factors.

Our large trial adds to the increasing evidence of tolerability and safety of pertussis vaccines in pregnancy established from large observational studies, randomized controlled trials, systematic reviews and *meta*-analyses [10,20,21,24–28,38–42]. We found no difference between the Tdap and control groups in the occurrence of obstetric or fetal complications or in the reported rates of AEs in mothers or infants. Of note, although chorioamnionitis was not selected as an AE of interest at the beginning of our study, during the study conduct several articles indicated a small but significant increased risk of chorioamnionitis [21,43,44]. In our trial, two women in the control and none in the Tdap group reported chorioamnionitis.

Our study has some limitations. Although this large trial provides definitive evidence for the primary outcome, it is limited by power to provide reliable conclusions for the rare AEs following immunization or adverse pregnancy outcomes. In addition, no adjustments for mul-

Table 2
Superiority assessment, GMCs and seropositivity rates of maternally transferred pertussis antibodies in infant cord blood of Tdap-vaccinated women versus control women (ATP cohort for immunogenicity).

Antibody (LLoQ)	Tdap group			Control group			Tdap/control
	N	% ≥ LLoQ (95% CI)	GMC, IU/mL (95% CI)	N	% ≥ LLoQ (95% CI)	GMC, IU/mL (95% CI)	GMC ratio[a] (95% CI)
Anti-FHA	29	100	366.1	29	96.6	22.7	16.1
(2.046 IU/mL)	1	(98.7–100)	(329.0–407.3)	2	(93.8–98.3)	(19.7–26.2)	(13.5–19.2)
Anti-PRN	29	99.7	301.8	29	88.0	14.6	20.7
(2.187 IU/mL)	0	(98.1–100)	(250.9–362.9)	1	(83.7–91.5)	(12.1–17.7)	(15.9–26.9)
Anti-PT	29	98.6	46.9	29	68.8	5.5	8.5
(2.693 IU/mL)	0	(96.5–99.6)	(41.2–53.3)	2	(63.2–74.1)	(4.8–6.3)	(7.0–10.2)

Abbreviations: % ≥ LLoQ, percentage of women for whom antibody concentrations in infant cord blood were greater than or equal to the assays' LLoQs; ATP, according-to-protocol; CI, confidence interval; FHA, filamentous hemagglutinin; GMC, geometric mean concentration; LLoQ, lower limit of quantitation; N, number of participants with available results; PRN, pertactin; PT, pertussis toxoid; Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.

[a] Superiority was reached if the lower limits of the 95% CIs of the GMC ratios (Tdap divided by control) for anti-FHA, anti-PRN and anti-PT antibodies were ≥ 1.5.

Table 3
Pertussis vaccine response 1 month post-vaccination and seropositivity rates and GMCs for pertussis antibodies before and 1 month post-vaccination in pregnant women (ATP cohort for immunogenicity).

Antibody (LLoQ)	Time point	Tdap group					Control group				
		N	Vaccine response[a]% (95% CI)	N'	% ≥ LLoQ (95% CI)	GMC, IU/mL (95% CI)	N	Vaccine response[a]% (95% CI)	N'	% ≥ LLoQ (95% CI)	GMC, IU/mL (95% CI)
Anti-FHA (2.046 IU/mL)	Pre	–	–	289	94.5 (91.2–96.8)	13.7 (11.8–15.8)	–	–	291	94.5 (91.2–96.8)	15.7 (13.6–18.0)
	Post	288	93.4 (89.9–96.0)	290	100 (98.7–100)	317.5 (285.0–353.8)	290	1.4 (0.4–3.5)	291	94.5 (91.2–96.8)	15.0 (13.1–17.2)
Anti-PRN (2.187 IU/mL)	Pre	–	–	289	84.4 (79.7–88.4)	11.1 (9.1–13.4)	–	–	290	85.2 (80.6–89.1)	11.3 (9.4–13.6)
	Post	288	89.6 (85.5–92.9)	290	100 (98.7–100)	283.6 (237.1–339.1)	290	0.7 (0.1–2.5)	291	84.5 (79.9–88.5)	10.5 (8.7–12.5)
Anti-PT (2.693 IU/mL)	Pre	–	–	288	58.0 (52.1–63.8)	4.0 (3.5–4.5)	–	–	291	63.2 (57.4–68.8)	4.3 (3.8–4.8)
	Post	287	87.8 (83.4–91.4)	289	98.6 (96.5–99.6)	45.6 (40.4–51.5)	291	1.0 (0.2–3.0)	292	61.3 (55.5–66.9)	4.1 (3.6–4.6)

Abbreviations: % ≥ LLoQ, percentage of women with antibody concentrations greater than or equal to the assays' LLoQs; -, not applicable; ATP, according-to-protocol; CI, confidence interval; FHA, filamentous hemagglutinin; GMC, geometric mean concentration; LLoQ, lower limit of quantitation; N, number of participants with pre- and post-vaccination results available; N', number of participants with results available at the specified time point; PRN, pertactin; PT, pertussis toxoid; Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.

[a] Vaccine response was defined as a post-vaccination antibody concentration ≥ 4 times the LLoQ for participants with a pre-vaccination antibody concentration below the LLoQ; a post-vaccination antibody concentrations ≥ 4 times the pre-vaccination concentration for participants with a pre-vaccination antibody concentration between the LLoQ and < 4 times the LLoQ; and a post-vaccination antibody concentration ≥ 2 times the pre-vaccination concentration for participants with a pre-vaccination antibody concentration ≥ 4 times the LLoQ.

Table 4
Seropositivity rates and GMCs of maternally transferred pertussis antibodies in infant cord blood of Tdap-vaccinated women versus control women, by gestational age at the pregnancy dose (ATP cohort for immunogenicity).

Antibody (LLoQ)	Gestational age at pregnancy dose	Tdap group			Control group		
		N	% ≥ LLoQ (95% CI)	GMC, IU/mL (95% CI)	N	% ≥ LLoQ (95% CI)	GMC, IU/mL (95% CI)
Anti-FHA (2.046 IU/mL)	27–32 weeks	184	100 (98.0–100)	403.6 (356.7–456.6)	172	95.3 (91.0–98.0)	20.3 (16.8–24.6)
	33–36 weeks	107	100 (96.6–100)	309.6 (254.3–376.9)	119	98.3 (94.1–99.8)	26.3 (21.1–32.7)
Anti-PRN (2.187 IU/mL)	27–32 weeks	183	100 (98.0–100)	386.6 (309.7–482.5)	171	87.7 (81.8–92.2)	13.6 (10.6–17.3)
	33–36 weeks	107	99.1 (94.9–100)	197.5 (144.1–270.7)	119	88.2 (81.0–93.4)	16.2 (11.9–22.0)
Anti-PT(2.693 IU/mL)	27–32 weeks	184	98.9 (96.1–99.9)	51.2 (43.6–60.0)	172	66.9 (59.3–73.8)	5.3 (4.5–6.3)
	33–36 weeks	106	98.1 (93.4–99.8)	40.2 (32.3–50.1)	119	71.4 (62.4–79.3)	5.8 (4.7–7.3)

Abbreviations: % ≥ LLoQ, percentage of women for whom antibody concentrations in infant cord blood were greater than or equal to the assays' LLoQs; ATP, according-to-protocol; CI, confidence interval; FHA, filamentous hemagglutinin; GMC, geometric mean concentration; LLoQ, lower limit of quantitation; N, number of participants with available results; PRN, pertactin; PT, pertussis toxoid; Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.

Table 5
Seroprotection rates and GMCs for diphtheria and tetanus antibodies before and 1 month post-vaccination in pregnant women (ATP cohort for immunogenicity).

Antibody	Time point	Tdap group			Control group		
		N	% ≥0.1 IU/mL (95% CI)	GMC, IU/mL (95% CI)	N	% ≥0.1 IU/mL (95% CI)	GMC, IU/mL (95% CI)
Anti-diphtheria	Pre	288	64.2 (58.4–69.8)	0.19 (0.16–0.22)	288	71.2 (65.6–76.3)	0.23 (0.19–0.27)
	Post	290	97.6 (95.1–99.0)	2.19 (1.87–2.57)	289	70.6 (65.0–75.8)	0.23 (0.19–0.27)
Anti-tetanus	Pre	289	95.8 (92.9–97.8)	0.92 (0.81–1.04)	291	96.6 (93.8–98.3)	1.05 (0.92–1.19)
	Post	290	100 (98.7–100)	8.43 (7.72–9.20)	292	96.6 (93.8–98.3)	0.98 (0.86–1.11)

Abbreviations: % ≥0.1 IU/mL, percentage of women with antibody concentrations greater than or equal to 0.1 IU/mL (seroprotection cut-off); ATP, according-to-protocol; CI, confidence interval; GMC, geometric mean concentration; N, number of participants with available results; Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.

tiplicity were made. The study was conducted in six high-income countries, mainly in white Caucasian pregnant women, hence the data may not be generalizable to other settings (low- and middle-income countries) or ethnicities. Also, the study results refer to healthy women with and infants born from low-risk pregnancies, with appropriate access to health care services and to childhood immunizations.

Some of the main strengths of our study include its single-blind, randomized, placebo-controlled design, its large sample size, ensuring high power to conclude on the primary objective, the high retention of participants (with 96% of women completing the study and 84% being included in the ATP analysis) and the high compliance in returning diary cards (>96%).

Table 6
Pregnancy outcomes, pregnancy-/neonate-related adverse events of interest and characteristics of infants at birth (total vaccinated cohort).

	Tdap group (N = 341)		Control group (N = 346)	
Outcome	n	% (95% CI)	n	% (95% CI)
Pregnancy outcomes[a]				
Live infant no apparent congenital anomaly	332	97.4 (95.0–98.8)	337	97.4 (95.1–98.8)
Live infant congenital anomaly[b]	9	2.6 (1.2–5.0)	8	2.3 (1.0–4.5)
Lost to follow-up	0	0.0 (0.0–1.1)	1	0.3 (0.0–1.6)
Pregnancy-/neonate related adverse events of interest[c]				
Intrauterine growth restriction/poor fetal growth	5	1.5 (0.5–3.4)	2	0.6 (0.1–2.1)
Pre-eclampsia	1	0.3 (0.0–1.6)	5	1.4 (0.5–3.3)
Pregnancy-related hypertension	4	1.2 (0.3–3.0)	5	1.4 (0.5–3.3)
Premature labor	13	3.8 (2.0–6.4)	11	3.2 (1.6–5.6)
Premature rupture of membranes	13	3.8 (2.0–6.4)	15	4.3 (2.4–7.0)
Premature uterine contractions	2	0.6 (0.1–2.1)	3	0.9 (0.2–2.5)
Preterm birth	11	3.2 (1.6–5.7)	9	2.6 (1.2–4.9)
Preterm premature rupture of membranes	4	1.2 (0.3–3.0)	7	2.0 (0.8–4.1)
Small for gestational age	2	0.6 (0.1–2.1)	2	0.6 (0.1–2.1)
Vaginal or intrauterine hemorrhage	9	2.6 (1.2–5.0)	10	2.9 (1.4–5.3)
Infant characteristics at birth		Value ± SD		Value ± SD
Mean weight, kg		3.3 ± 0.5		3.4 ± 0.4
Mean head circumference, cm		34.6 ± 1.7		34.8 ± 1.3
Mean Apgar score 1 min		8.8 ± 1.1		8.8 ± 1.2
Mean Apgar score 5 min		9.5 ± 0.6		9.5 ± 0.6

Abbreviations: CI, confidence interval; N, number of vaccinated participants per group; n/%, number/percentage of participants reporting the specified event; SD, standard deviation; Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.
[a] There were no stillbirths or elective terminations.
[b] Additional congenital anomalies were reported in the follow-up studies (NCT02422264 and NCT02853929) if they became apparent after the current study ended.
[c] No maternal or neonatal deaths, gestational diabetes, eclampsia, neonatal hypoxic-ischemic encephalopathy, failure to thrive or growth deficiencies were observed in either of the groups.

Table 7
Solicited and unsolicited adverse events after the pregnancy and post-delivery doses (total vaccinated cohort).

	Pregnancy dose				Post-delivery dose			
	Tdap group (N = 335) (received Tdap)		Control group (N = 343[a]) (received placebo)		Tdap group (N = 324) (received placebo)		Control group (N = 330[a]) (received Tdap)	
Adverse event	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Solicited local AEs (8 days post-vaccination)								
Pain								
Any	289	86.3 (82.1–89.8)	50	14.6 (11.0–18.8)	41	12.7 (9.2–16.8)	207	62.7 (57.3–68.0)
Grade 3	7	2.1 (0.8–4.3)	0	0.0 (0.0–1.1)	2	0.6 (0.1–2.2)	14	4.2 (2.3–7.0)
Redness								
Any	96	28.7 (23.9–33.8)	44	12.8 (9.5–16.8)	34	10.5 (7.4–14.4)	98	29.7 (24.8–34.9)
>50 mm	3	0.9 (0.2–2.6)	0	0.0 (0.0–1.1)	0	0.0 (0.0–1.1)	3	0.9 (0.2–2.6)
Swelling								
Any	84	25.1 (20.5–30.1)	12	3.5 (1.8–6.0)	17	5.2 (3.1–8.3)	87	26.4 (21.7–31.5)
>50 mm	3	0.9 (0.2–2.6)	0	0.0 (0.0–1.1)	0	0.0 (0.0–1.1)	4	1.2 (0.3–3.1)
Solicited general AEs (8 days post-vaccination)								
Fatigue								
Any	146	43.6 (38.2–49.1)	124	36.3 (31.2–41.6)	130	40.1 (34.7–45.7)	153	46.2 (40.8–51.8)
Grade 3	6	1.8 (0.7–3.9)	5	1.5 (0.5–3.4)	24	7.4 (4.8–10.8)	36	10.9 (7.7–14.7)
GI symptoms								
Any	60	17.9 (14.0–22.4)	52	15.2 (11.6–19.5)	32	9.9 (6.9–13.7)	42	12.7 (9.3–16.8)
Grade 3	3	0.9 (0.2–2.6)	3	0.9 (0.2–2.5)	6	1.9 (0.7–4.0)	5	1.5 (0.5–3.5)
Headache								
Any	83	24.8 (20.2–29.8)	78	22.8 (18.5–27.6)	75	23.1 (18.7–28.1)	78	23.6 (19.1–28.5)
Grade 3	4	1.2 (0.3–3.0)	3	0.9 (0.2–2.5)	5	1.5 (0.5–3.6)	4	1.2 (0.3–3.1)
Fever								
Any	4	1.2 (0.3–3.0)	3	0.9 (0.2–2.5)	15	4.6 (2.6–7.5)	30	9.1 (6.2–12.7)
>39.0 °C	0	0.0 (0.0–1.1)	0	0.0 (0.0–1.1)	3	0.9 (0.2–2.7)	1	0.3 (0.0–1.7)
Unsolicited AEs (31 days post-vaccination)								
		(N = 341)		(N = 346)		(N = 336)		(N = 342)
Any	132	38.7 (33.5–44.1)	123	35.5 (30.5–40.8)	103	30.7 (25.8–35.9)	110	32.2 (27.2–37.4)
Grade 3	23	6.7 (4.3–9.9)	10	2.9 (1.4–5.3)	17	5.1 (3.0–8.0)		6.1 (3.8–9.2)
Vaccine-related	8	2.3 (1.0–4.6)	11	3.2 (1.6–5.6)	5	1.5 (0.5–3.4)	21	2.0 (0.8–4.2)

Abbreviations: AE, adverse event; CI, confidence interval; GI, gastrointestinal; N, number of vaccinated participants (for unsolicited AEs) or number of participants with documented dose (solicited AEs); n/%, number/percentage of participants reporting the event at least once; Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine.
[a] For solicited general AEs, N = 342 for the pregnancy dose and N = 331 for the post-delivery dose. Grade 3 pain was defined as significant pain at rest or pain preventing normal activities; fatigue, GI symptoms, headache and unsolicited AEs were considered grade 3 if they prevented normal activities.

The long-term safety outcomes of the infants born to mothers in our current study, persistence of pertussis antibodies to 2–3 months of age and the effect of maternal Tdap immunization on infant immune responses to and safety of primary and booster DTaP vaccination in the child's first 18 months of life are assessed in two follow-up studies (NCT02422264 [45] and NCT02853929).

5. Conclusion

This placebo-controlled randomized trial, currently the largest on pertussis vaccination during pregnancy, brings additional evidence for maternal pertussis immunization providing high levels of transplacental antibodies to infants for protection against pertussis disease during the vulnerable newborn period. This study adds a substantial amount of high-quality safety data on pregnancy outcomes and pregnancy-/neonate-related AEs. Our data support the recommendation for routine Tdap immunization in pregnancy to improve protection of infants against pertussis disease prior to primary infant immunization.

6. Contributors

BC, ICG, KPP, MBEP, MCFM, OGV, SAH, SOK and TN were involved in study conception and design.

AMG, BT, CMP, FMT, GVZ, ICG, JEAF, KPP, LK, MBEP, MAC, MARZ, MDCM, MMF, MV, NMes, NMey, OGV, PGM, PK, PM, SAH, SOK, TN, YRE and ZS performed the study and participated in data collection.

ICG, KPP, LK, MBEP, MAC, MV, NMes, NMey, SAH, SOK and TN were involved in data analysis and interpretation.

KPP wrote the manuscript and all authors have revised and approved the manuscript.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BC, MAC, NMes, NMey and SOK are employees of the GSK group of companies (GSK), and BC and NMes own GSK restricted shares. BT, MBEP, OGV, SAH and TN's institutions received grants from GSK during the conduct of the study. KPP received grants from the National Health and Medical Research Council during the conduct of the study, and from MedImmune, Novavax and Pfizer outside the submitted work. FMT's institution received financial support from GSK during the conduct of the study, as well as financial and non-financial support outside the submitted work; he also received personal fees from Pfizer, Novavax, MSD and Sanofi Pasteur; his institution also received financial support as trial fees from Ablynx, Jansen, Regeneron, Medimmune, Pfizer, MSD, Sanofi Pasteur, Novavax and Novartis, as well as non-financial support from Pfizer and MSD and grants from MSD and Astra Zeneca. LK is working as consultant for GSK. SAH is member of ad-hoc advisory committees for GSK and Sanofi Pasteur and he has a patent for novel triple adjuvant issued. AMG, CMP, GVZ, ICG, JEAF, MARZ, MCFM, MDCM, MMF, MV, PGM, PK, PM, YRE and ZS declare no conflicts of interest.

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Data sharing statement

The study protocol is available at https://www.gsk-studyregister.com/study/4898. Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Trademarks

Boostrix is a trademark of the GSK group of companies.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.10.105.

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