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TITLE:
Safety of Tdap vaccine in pregnant women: an observational study

ABSTRACT:
OBJECTIVES: Actively recruit and intensively follow pregnant women receiving a dose of acellular pertussis vaccine for 4 weeks after vaccination. DESIGN AND SETTINGS: A prospective observational study conducted in 2 New Zealand regions. PARTICIPANTS: Women in their 28th–38th week of pregnancy, recruited from primary care and antenatal clinics at the time of Tdap administration. Telephone interviews were conducted at 48 h and 4 weeks postvaccination. MAIN OUTCOMES MEASURES: Outcomes were injection site reactions, systemic symptoms and serious adverse events (SAEs). Where available, data have been classified and reported according to Brighton Collaboration definitions. RESULTS: 793 women participated with 27.9% receiving trivalent inactivated influenza vaccine concomitantly. 79% of participants reported mild or moderate pain and 2.6% severe pain. Any swelling was reported by 7.6%, induration by 12.0% (collected from 1 site only, n=326), and erythema by 5.8% of participants. Fever was reported by 17 (2.1%) participants, 14 of these occurred within 24 h. Headache, dizziness, nausea, myalgia or arthralgia was reported by <4% of participants, respectively, and fatigue by 8.4%. During the study period, there were 115 adverse events in 113 participants, most of which were minor. At the end of the reporting period, 31 events were classified as serious (eg, obstetric bleeding, hypertension, infection, tachycardia, preterm labour, exacerbation of pre-existing condition and pre-eclampsia). All had variable onset time from vaccination. There were two perinatal deaths. Clinician assessment of all SAEs found none likely to be vaccine related. CONCLUSIONS: Vaccination with Tdap in pregnant women was well tolerated with no SAE likely to be caused by the vaccine. TRIAL REGISTRATION NUMBER: ACTRN12613001045707.

Introduction:
In 2011, the US Advisory Committee on Immunization Practices (ACIP) recommended that acellular pertussis-containing vaccine (Tdap) be given to any person, including pregnant women, likely to be in contact with infants under the age of 12 months.1 In September 2012, the UK recommended providing Tdap vaccine for pregnant women ideally between 28 and 38 weeks of pregnancy.2 Vaccine administration in pregnancy offers maternal protection against pertussis and also provides for maternal antibody to be passed to the infant, which has been demonstrated to be protective in their first months of life.3
4 There are no theoretical safety concerns with administering subunit vaccines in pregnancy and some vaccines, in particular tetanus, have been used widely in pregnant women.5 In October 2012, in response to a pertussis epidemic, the New Zealand (NZ) Ministry of Health began funding Tdap vaccine for all women from 28 to 38 weeks gestation.
While there are now several large studies published,6–10 at the time of this study, the USA ACIP committee acknowledged that the safety of Tdap immunisation during pregnancy had not been systematically studied, with the only data available coming from small studies, postmarketing surveillance, and the US Vaccine Adverse Event Reporting System.1
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Our aim was to intensively monitor the safety of Tdap vaccine in a larger group of pregnant women for a period up to 4 weeks postvaccination.

Study design, setting and participants ::: Methods:
This was a prospective observational study conducted in two different geographical areas of NZ using the same outcome measures and database. There was some difference in recruitment and data collection methods. The Northern arm of the study was conducted primarily in Auckland and included other North Island centres. Auckland is a culturally diverse metropolitan city of 1.42 million in the North Island. Women being administered Tdap between 28 and 38 weeks gestation were identified by staff from 21 out of 24 participating general practices and the maternity clinics of three district health boards (DHBs) and referrals faxed to the study team from 30 January to 30 June 2014.
The other arm was conducted in Canterbury, a more ethnically homogeneous South Island region of just over half a million. Recruitment for this arm began earlier, from late September 2012 to late June 2014. Participants aged 18–40 years and administered Tdap between 30 and 36 weeks

gestation were identified via claims submitted by general practices (within 1 week of vaccination) for reimbursement from the local DHB for each vaccination service delivered.
In both study arms, consent to be contacted by members of the research team was sought at the time of vaccination.
Inclusion criterion was being compliant with routine antenatal care, including at least one ultrasound early in pregnancy. Women who had given birth prior to being contacted by study team members were originally to be excluded from both arms of the study; however, owing to concern that this may lead to overlooked serious adverse events (SAEs; ie, premature birth) early in the study, after the first exclusion, subsequent women in the Northern arm who had birthed prior to contact but met other inclusion criteria were included.

Vaccines ::: Methods:
The pertussis-containing vaccine (Tdap) funded for pregnant women in NZ is Boostrix. The Boostrix formulation used in NZ has 0.5 mg aluminium as aluminium hydroxide and aluminium phosphate adjuvant and the US formulation has no more than 0.39 mg aluminium as aluminium hydroxide.
Influenza (TIV) vaccine is given at the start of the winter season and funded for all pregnant women regardless of gestational age. Where this time coincides with the gestation age for delivery of the Tdap, providers are encouraged to deliver both vaccines together.

Data collection and main outcomes ::: Methods:
Northern participants leaving the practice/clinic after their vaccination were given a study envelope containing an information sheet, consent form, clear plastic measuring tool (to measure any local reaction) and a 3-day diary card to record any symptoms or events. At the first phone contact 48–72 h postvaccine administration, verbal consent was obtained and an interview undertaken. The second phone interview was conducted at 4 weeks postadministration (see figure 1).
For Canterbury participants, a research team member made phone contact with potential participants within 2 weeks of identification, obtained consent and conducted the first interview. A follow-up questionnaire was mailed at 4 weeks postvaccination.
For both groups, consent to follow-up with their Lead Maternity Carer (either a midwife or obstetrician) or general practitioner was sought from all women who reported an SAE or any birth complication. As per national protocols,12 any adverse events (AEs) were also reported to the Centre for Adverse Reaction Monitoring (CARM), the official regulatory body in charge of receiving all AE reports in NZ. An AE is any untoward medical occurrence temporally associated with administration of the vaccine and does not include common injection site reactions. In NZ, AEs following immunisation reporting is encouraged if the event is serious or unexpected. Anonymised data for any SAEs were also reported to the Marketing Authorisation Holder (the vaccine manufacturer) as part of global drug safety surveillance.
To ensure consistency in our classifications of SAEs, we used an algorithm based on the International Conference on Harmonisation definitions for SAEs.13
14 We separated events occurring in the mother during pregnancy (figure 2) and those triggered by indications of non-reassuring fetal status (figure 3).
An SAE is defined as any untoward medical occurrence that: results in death; is life-threatening; requires inpatient hospitalisation or causes prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or requires intervention to prevent permanent impairment or damage.
The term ‘life threatening’ used here refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.15
All SAEs were followed up by a study clinician.

Solicited and unsolicited outcomes ::: Methods:
The diary card (Northern arm) allowed recording of injection site reactions, fever and unsolicited events over 3 days (days 0, 1 and 2). Response categories were consistent with Brighton Collaboration definitions and guidelines for events following immunisation.16–19
The 48 h postvaccination telephone interview (Northern arm) asked about nausea, vomiting, diarrhoea, headache, fatigue and contact with healthcare services. Participants were also asked if they had any other concerns after the vaccination. The telephone interview conducted by the Canterbury team sought the same information retrospectively for up to 7 days postvaccination.

The 4-week postvaccination telephone interview (Northern arm) and mailed questionnaire (Canterbury arm) asked if any events, including contact with health professionals, had occurred since the last interview. Canterbury participants were phoned if their questionnaire was not returned.

Statistical analysis ::: Methods:
The size of our sample was based on the number of births in the study regions (28 000 per annum), estimated uptake of pertussis vaccine in pregnancy and the number of women available for follow-up over the study time frame.
Since the two regions recruited and collected data in different ways, we have not attempted to analyse any differences.
Frequencies, percentages and cross-tabulations for demographic and outcome variables were produced using SAS Enterprise Guide V.6. Results are summarised as counts and percentages for each outcome. Values within outcome variables (eg, pain, redness, swelling and induration) are based on Brighton Collaboration definitions of outcomes. Other outcomes, such as fever, nausea and myalgia, are summarised as presence or absence (ie, yes or no). Missing values are reported in the tables where relevant.

Injection site reactions ::: Results:
Pain was the most commonly reported reaction to the Tdap injection with 79.0% of participants overall reporting mild or moderate pain in total. Severe pain was reported by 2.6%. Onset of pain occurred within 24 h in 83.9% of participants. There were differences in the intensity, onset and resolution. Northern study participants reported higher intensity pain, later onset and longer time until resolution (table 2). The proportion reporting no pain was similar for both groups.
Swelling at the injection site was uncommon with 7.6% of participants reporting any swelling and three participants (0.4%) reporting swelling greater than 5 cm. All cases of swelling had an onset within 48 h with half unresolved after 48 h (table 3). The timing of onset of swelling reported was different between the two study populations with 94% of the Southern population reporting the onset of swelling within 24 h compared with 48% of the Northern population. The time to resolution was the same in both groups with 49% resolving within 48 h (not shown).
Erythema was reported by 5.8% of participants with 0.4% reporting erythema of greater than 5 cm. Onset was generally within 48 h and resolution over 48 h for half of these (table 3). While there were 37 reports of erythema for the Northern participants, there were 9 reports for the Southern participants.
Induration as an injection site reaction was collected in the Northern but not the Canterbury arm. Any induration was reported by 12% of participants, of whom half took more than 48 h to resolve. No induration events measured greater than 5 cm (table 3).

Systemic events ::: Results:
Fever was reported by 17 (2.1%) participants, 14 of whom reported this occurring within 24 h. Of those reporting fever within 24 h, 6 (35%) had been co-administered influenza vaccine (table 4). There were 10 reports of fever in the Northern participants and 7 reports in the Southern participants, and 6/10 Northern participants and 0/7 Southern participants were co-administered influenza vaccine.
Other systemic events included headache and dizziness, nausea and vomiting, fatigue and myalgia or arthralgia. All were uncommon and reported by fewer than 4% of participants with the exception of fatigue, which was reported by 8.4% (table 5). Thirty-two participants reported more than one of these outcomes occurring together. Around one-quarter to one-third of those who reported a systemic event also received the influenza vaccine at the same time (table 5).

AEs and SAEs ::: Results:
During the study period, there were 115 AEs and SAEs in 113 participants (two events each for two participants) reported to CARM, in accordance with local guidelines. CARM reports submitted for events not considered as SAEs were mostly minor in nature and for a range of issues including a stiff neck on the same side as the injection, itching, changes in baby movements and combinations of systemic events such as headaches, nausea, fatigue and fever (see tables 4 and 5). Additionally, 25 reports were for diagnosed non-injection site infections (eg, chest, urine and throat).
We have reported SAEs according to whether they occurred or were triggered during pregnancy; during labour and delivery; or occurred in the infant after delivery.

Of the 31 events deemed to be serious (3.9%), there were 23 hospitalisations following immunisation that occurred during pregnancy. Reasons for these were: obstetric bleeding (4), hypertension (2), infection (4), tachycardia (1), preterm labour (9), exacerbation of pre-existing condition (2) and pre-eclampsia (1). All had variable onset time from vaccination (table 6). Additionally, there were a total of eight SAEs that occurred during labour and delivery: six reported in the Northern arm and two in the Canterbury arm (note the different methodologies). Of these eight SAEs,
two were perinatal deaths, one of which was due to a congenital abnormality, the other unexplained. There was one cyanotic episode and five cases where concern for fetal well-being resulted in health service intervention (table 7).

Discussion:
Reduced-antigen-content tetanus–diphtheria–acellular pertussis (Tdap) vaccines have been shown to be highly effective in pregnancy for reducing infant pertussis morbidity,3
4 and are being increasingly recommended on national schedules, particularly during epidemics. While there have been no safety concerns to date using these vaccines in pregnancy, data on safety in pregnancy are relatively limited. This study intensively followed 793 women vaccinated in pregnancy with Tdap for solicited and unsolicited outcomes. Our sample included pregnant women regardless of underlying conditions, including women with comorbidities. Injection site reactions were common, minor and self-limiting. Systemic reactions were uncommon. Differences in pain reporting between the study groups are likely due to both demographic differences and differences in data collection methods. Since there was delay in interviewing the Southern participants and no participant-held diary, minor events are possibly prone to recall bias. Previous NZ studies have shown that vaccine reactogenicity varies by ethnic group.20
21 SAEs occurred in our study population during the study period. None were likely to have been caused by the exposure to Tdap vaccine.
Since this is an observational study with no direct comparator groups, the size of the study has limited power to detect SAEs. Data collection methods and periods for each region were different and the Northern region included a wider gestational age band. While our results add to the body of evidence of safety for pregnant women, the study population was not randomly selected. The women in our group were older (32 vs 29.2 years) and more likely to be of NZ European ethnicity (73.5% vs 49.5%) than the general NZ maternal population. This is most likely a reflection of the health-seeking behaviour associated with these demographics. While pregnancy complications increase with age, in contrast, NZ European ethnicity is associated with lower risk pregnancies.22
The reactogenicity of acellular pertussis-containing vaccines in adults was reviewed in 2012.23 Data on the reactogenicity of Tdap are derived from clinical trials and prospective studies; however, the results are not presented in a standardised way that allows for comparison. There is insufficient information in the study manuscripts to determine in more detail how events are measured or classified. However, severe local pain ranges from less than 1% to 30%, and severe local redness or swelling (≥50 mm) ranges from 2% to 18%.24–30 Although most of these studies were published after 2007 when definitions were published by the Brighton Collaboration, none have provided information about induration.
A small US randomised trial including 33 pregnant women assessed the immunogenicity and safety of Tdap during pregnancy. Safety outcomes were collected with a 7-day diary. How these were defined is not described. Pain was reported by 25 (75.8%) participants while erythema and induration/swelling were each reported by 3 (9.1%) participants. These were the same rates as reported by the non-pregnant women in the study.31 The rates of injection site pain in our study are consistent with most other studies that report less than 10% experiencing severe pain.16
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28 Rates of swelling with a diameter of more than 50 mm ranged from 1% to 18% in clinical studies. In our study population, just 0.4% recorded a swelling of more than 50 mm and fewer than 8% reported any.16
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30 Our outcomes are lower than these other reports; however, this could be because we have differentiated between swelling and induration. Overall, both events were infrequent and mild. Erythema (redness) was relatively uncommon in our study with fewer than 6% of participants reporting any and 1.4% reporting a diameter greater than 50 mm. In clinical studies, severe erythema has been reported to range from 2% to 17%.24–28

30 Our rates are consistent with those recently reported in the US trial in pregnant women.31 It should be noted that the aluminium content of the NZ Boostrix formulation is higher than that of the US formulation, and the higher aluminium content may be linked to greater local reactogenicity.32

In the Northern arm of our study, we collected information about swelling and induration according to Brighton Collaboration definitions17

18 and are able to report induration separately from swelling. Induration occurred more frequently than swelling and appeared to have a later temporal onset than swelling. More than half of the cases of induration occurred 25–48 h later compared with around a quarter of all swellings, supporting the likelihood that each has a different aetiology. It is likely that some of the swelling reported in the Southern participants was in fact induration misclassified.

We found differences in the reporting of swelling and erythema between our groups. There were fewer reports of erythema in the Southern group, and while there were similar numbers of reports of swelling, the timing for onset may have been more imprecise. Given the differences in the reported pain onset and resolution between the groups, it is likely that recall for details of minor local reactions became more prone to recall bias as time progressed and in the absence of a diary to record the details.

While in previous clinical studies headache has tended to be reported by around a third of participants,24

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27–30 fewer than 3.9% of our participants reported either headache or feeling dizzy. Also, few of our participants reported any gastrointestinal symptoms (2.8%). Almost all systemic events in our study occurred in the 24 h following immunisation as opposed to later, and we consider them likely to be vaccine related. Overall, there were few systemic events reported and the rates of the most common are consistent with those reported in the US study with 33 participants.31 In our study, one-third to one-quarter of those who reported systemic events had also received the influenza vaccine at the same time. Northern participants reporting systemic events were consistently more likely to have received co-administered influenza vaccine than Southern participants. Most of the reported fevers in our Northern participants also occurred after co-administration with influenza vaccine. Some influenza vaccines are known to be more pyrogenic than others, so it is possible that influenza vaccine was the cause of these excess reports, particularly as the fevers occurred within 24 h after vaccination.21 The safety of co-administration of influenza vaccine and Tdap in pregnancy has been assessed by the Vaccine Safety Datalink Project, and no excess medically attended events occurred among women receiving both vaccines together compared with sequential vaccination.6 However, it cannot be assumed that these vaccines have the same reactogenicity profiles.

SAEs occurred in our study population during the study period. None were considered by clinical review as likely to be caused by the exposure to Tdap vaccine. In NZ, up to 15% of pregnancies have obstetric complications, and approximately 1 per 10 infants are born preterm or low birth weight.33

34 Annually, there are approximately 600 perinatal deaths (~1% of births) of which 14% are unexplained. These figures have remained consistent over time.22 On the basis of NZ data, the rates of SAEs in our study were not higher than the expected background rate for such a cohort. Reports to the US Vaccine Adverse Event Reporting System of pregnant women inadvertently given Tdap have been summarised.35 Between January 2005 and June 2010, there were 132 reports identified, 20 following Boostrix with no non-pregnancy SAEs reported. In the US trial,31 SAEs occurred in 7/33 pregnant women, without known risks to pregnancy at enrolment, followed to 4 months postpartum, and none of these were non-pregnancy SAEs. The events occurred at variable time periods following immunisation and none were considered attributable to the vaccine. Recently, obstetric events and birth outcomes for 123 494 women from two Californian Vaccine Safety Datalink sites were evaluated; 26 229 women received Tdap with no increased risk for hypertensive disorders of pregnancy or preterm or small for gestational age birth found. There was a small increased risk of chorioamnionitis diagnosis.9 Further investigations have not found an association.7

8 A matched cohort study from the UK in 20 074 pregnant women and a matched historical unvaccinated control group found no evidence of any increase for predefined pregnancy-related AEs including stillbirth.10 These studies all support the safety profile of Tdap in pregnancy.

In conclusion, we found that a Tdap vaccination was well tolerated in pregnant women. Our findings are consistent with data from studies involving non-pregnant women.23 There were no

SAEs in this study that were likely to have been caused by the vaccine. This is reassuring for pregnant women, vaccinators and policymakers.