Pertussis in Pregnancy Safety (PIPS) Study

Protocol

A three-component observational study to assess the safety of pertussis vaccine (Tdap) administered during pregnancy

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Project sponsors

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Signature page

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Abbreviations

AE	Adverse Event
CARM	Centre for Adverse Reaction Monitoring
DHB	District Health Board
ESR	Environmental and Scientific Research
GP	General Practice/General Practitioner
MoH	Ministry of Health
NHI	National Health Index Number
NIR	National Immunisation Register
NMD	National Minimum Dataset
PMS	Practice Management System
SAE	Serious Adverse Event

Section 2: Research

Overview

Aims

To evaluate health outcomes in infants of mothers vaccinated with Tdap during pregnancy.
To describe adverse events in pregnant women who received Tdap vaccine.

Objectives

Whole birth cohort (Study One)

To establish background rates for key endpoints in pregnant women and their infants

- Secondary objective 1: To examine the difference in hospital-related outcomes of those vaccinated or not with Tdap during pregnancy in all NZ women pregnant between 2009 and 2013.
- Secondary objective 2: To examine the difference in birth outcomes and hospital-related outcomes of infants born to mothers vaccinated or not with Tdap during pregnancy in all NZ women pregnant between 2009 and 2013.

Intensive safety monitoring (Study Two)

To intensively follow up a subgroup of NZ women who received pertussis-containing vaccine, during pregnancy for a period of one month after vaccine administration and document health outcomes for vaccinees for this period.

Intensive safety monitoring (Study Three) *Canterbury District Health Board (DHB), Tony Walls (PI)*

To describe adverse events in women who were administered Tdap under the DHB programme between 30–36 weeks of gestation
To describe outcomes of babies whose mothers were vaccinated with Tdap in the Canterbury region during week 30 to 36 of pregnancy (including birth history, weight and head circumference and any congenital abnormalities

Clinical hypothesis

The rates and patterns of adverse events following administration of Tdap during pregnancy (including the rates and patterns of any adverse pregnancy outcome, and the outcomes in infants up to one year of age), are similar to those where no vaccination during pregnancy occurred.

Background

New Zealand (NZ) is currently experiencing a significant increase in pertussis. The number of notified cases has risen dramatically from July 2011 and remained high throughout 2012. Increases in pertussis notifications have been seen previously and occur over a four- to five-year cycle in NZ. The underlying reasons for such a cycle are unknown.

Notification data and associated rates by age indicate that the under-one-year-olds are the most vulnerable with a cumulative notification rate in 2012 of 606 per 100,000 or 378 cases, 167 being hospitalised. This is the highest cumulative notification rate of any age group in 2012. There were 40 notifications of infants under six weeks old, 36 of which were hospitalised.

In 2012 (up to 23 November) 287 hospitalisations were reported. Of these, 167 (58.2%) were infants under one year old. Two deaths were reported, one in a three-year-old unimmunised child with underlying health conditions, and one in an infant aged less than six weeks with a history of preterm birth. All infants hospitalised with pertussis infection younger than six weeks of age have not received their first pertussis immunisation. Data in NZ shows about 20% of infant cases are infected by their mothers.[1]

The most recent data for the two surveillance weeks (24 November–7 December 2012) showed 248 new cases of pertussis (113 and 135 cases, respectively) notified, including 111 confirmed cases, 92 probable cases, 14 suspect cases, and 31 cases still under investigation. Twenty-nine (11.7%) of the notified cases were aged less than one year. Fourteen cases were hospitalised.

Infants remain susceptible to pertussis until they have responded immunologically to the primary series of infant pertussis immunisations. As immunity (measured as serum antibody) derived from both natural infection and vaccination wanes over several years, most mothers pass little protective antibody via transplacental transfer to their unborn infant. However when present, pertussis IgG has been demonstrated to be effectively transferred from mother to infant.[2]

Recently the US Advisory Committee on Immunization Practices (ACIP) recommended that acellular pertussis vaccine (Tdap) be given to any person likely to be in contact with young infants under the age of 12 months, including pregnant women.[3] Administering the vaccine to pregnant women is advised because it not only offers protection to the mother from pertussis but as a result of the maternal booster response provides for maternal antibody to be passed to the infant, which may be protective for the first few weeks of life.

There are no theoretical safety concerns with administering subunit vaccines to pregnant women and some vaccines, such as tetanus, are used widely in this group. ACIP acknowledged that the safety of Tdap immunisation during pregnancy has not been systematically studied, with the only data available coming from small studies, post-marketing surveillance, and the US Vaccine Adverse Event Reporting System (VAERS).[4] They concluded that

[1] Walls R. Pertussis (whooping cough) epidemiology in Waikato, New Zealand: 2000–2009. *NZ Med J* 2011;124(1332).
[2] Leuridan E, Hens N, Peeters N, de Witte L, Van der Meeren O, Van Damme P. Effect of a prepregnancy pertussis booster dose on maternal antibody titers in young infants. Pediatric Infectious Disease Journal 2011 Jul;30(7):608-10.
[3] United States Centers for Disease Control and Prevention. Updated recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; 60(41): 2011
[4] US Advisory Committee on Immunization Practices. Summary Report. Atlanta, Georgia: ACIP; February 23-24, 2011. Available from http://www.cdc.gov/vaccines/recs/acip/downloads/min-feb11.pdf Accessed 23 April 2012.

available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine.

The NZ Ministry of Health's (MoH) Immunisation Technical Forum (ITF) on vaccines reviewed this recommendation in 2011 and recommended the use of Tdap during pregnancy in NZ (after 20 weeks gestation and preferably prior to 36 weeks).[5] The MoH also recommends and funds (the vaccine is given at no cost to the woman) influenza vaccination for all pregnant women in NZ.[6] In 2012, some DHBs in NZ agreed to fund the administration of Tdap during the current pertussis outbreak to pregnant women (30-36 weeks) and to women in the first two weeks after birth.[7] In October this was extended nationally by the MoH to all women from 28 to 38 weeks gestation for the duration of the epidemic. For General Practices to be paid for administering the vaccines the electronic Practice Management System (PMS) automatically messages through to a central administration centre (Healthpac) once the details of the vaccination have been entered.

As there are limited data on the use of Tdap in pregnant women, NZ is well placed to monitor the safety outcomes in this group.

This study incorporates a study that is currently underway in Canterbury NZ (referred to herein as Study Three[8]—see detail below), assessing the outcomes of mothers receiving Boostrix® in pregnancy and their infants up to a year after the birth. It will also provide an infrastructure for another proposed study assessing the antibody response to the primary vaccination series with Infanrix-hexa in infants born to mothers vaccinated with Boostrix® during pregnancy.

This is a three-component observational study that will collect data both retrospectively and prospectively. Data for all pregnant women and their infants in NZ between 2009 and 2013 will be obtained and pertussis vaccine exposure during pregnancy verified (Study One). Two sub-studies will actively follow mothers who received Tdap during pregnancy with one also following their infants for one year after birth (Study Two and Three).

Study One will involve de-identified data linkage for all pregnant women and their infants for the period 2009–2013 and the intensive monitoring studies (i.e., Study Two and Three) will prospectively follow up the mother for one month after vaccination (Study Two) with a further group being followed for both maternal and infant outcomes for one year from the birth of the infant (Study Three).

The large retrospective component to this study adds significant power to the overall study: It is a cost effective method of data collection and enables more effective assessment of seasonality. It will also provide data on a range of pregnancy and birth outcomes which are not readily available from a prospective study design (e.g., Apgar scores).

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[5] New Zealand Ministry of Health. Current advice on the public health management of pertussis. Wellington: MoH; 5 April 2012. Available at http://www.nzdoctor.co.nz/media/1682109/pertussis_letter_moh_5_apr_2012.pdf

[6] New Zealand Ministry of Health. Chapter 15: Influenza. In Immunisation Handbook 2011. Wellington: MoH; 2011. Available at http://www.google.co.nz/url?sa=t&rct=j&q=ministry%20health%20influenza%20vaccine%20pregnant%20women%20funded%20&source=web&cd=7&ved=0CGYQFjAG&url=http%3A%2F%2Fwww.health.govt.nz%2Fsystem%2Ffiles%2Fdocuments%2Fpublications%2F15influenza.pdf&ei=8SiWT8iDH4_m8QOgnNGMCg&usg=AFQjCNFUuAYDXQKxJFmtqXKd4PBfzm1i2A

[7] Canterbury District Health Board. Media release from Canterbury DHB: Free whooping cough vaccine extended to pregnant women. Christchurch: CDHB; April 19, 2012.

[8] Study Three is largely funded by Canterbury DHB, but is being conducted as part on the three-component study covered in this protocol. Study Three runs as per Study Two, except the former study will follow women and their infants for a period of one year after the birth of the infant while the follow up for the latter study is to four weeks post vaccination.

Study design

Study One: Retrospective analysis of safety outcomes for pregnant women vaccinated with TdaP vaccine and their infants.

Study population

All women delivering in NZ for the study period 2009–2013 and their infants will form the overall study population. Study One will identify all pregnancies and all exposures (except the very few who privately purchased the vaccine).

Note that in NZ, TdaP has been recommended in pregnant women between 20 and 36 weeks gestation since 2011 but had to privately purchase. In October 2012, the MoH recommended and began fully funding TdaP nationally for pregnant women who were between 28 and 38 weeks gestation. There will be some variation, mainly prior to this date as some women will have received it both earlier and later than this in a range of regionally funded programmes. We are able to identify these exposures in the regionally funded programmes. We will not be able to identify private purchase. We know from anecdotal evidence that the number of women purchasing prior to funded programmes was very low but we cannot accurately quantify. GSK NZ have followed this up and confirm very few doses.

While TdaP was available via fee-for-service as early as 20 weeks gestation, a selection of DHBs began funding TdaP in pregnant women in 2012. Each DHB decided the gestation period required to receive funded TdaP. For example, Counties Manukau DHB-funded TdaP for women after 20 weeks gestation while Canterbury DHB funded TdaP for women between 30 and 36 weeks gestation. Again, these exposures can be identified.

Study participants

Hospitalisation data for the study period will be obtained from the National Minimum Dataset. Health outcomes in the study population that required contact with a hospital will be described for mothers by health outcome type and incidence per maternal age, ethnicity, deprivation, vaccination exposure and time interval from vaccination. For infants the health outcomes in the study population that required contact with a hospital will be described by infant ethnicity, age, deprivation, maternal age, ethnicity and deprivation and whether or not vaccination was given during pregnancy. The data for infants included in Study One will include the first year of life.

Vaccination status will be determined through the claims information submitted to the DHB and matched to the hospitalisation data. Notifications for pertussis will be determined from Environmental Science and Research (ESR) who provide disease surveillance to the government. ESR, under contract to the MoH, undertakes laboratory based surveillance of notifiable diseases and outbreak surveillance. Hospitalisations will be determined through the National Minimum Dataset. Hospitalisations and notifications will be matched to vaccine status using the National Health Index Number (NHI).

All participants in this study will be de-identified.

Outcomes

Hospitalisation outcomes of interest will include the following conditions.

Mother	**ICD-10-CM**
Still birth, preterm birth pregnancy complications	P95 Stillbirth[9] O60 Preterm labour Z37 Outcome of delivery • Single stillbirth • Twins, one liveborn and one stillborn • Twins, both stillborn • Other multiple births, all stillborn O00-O99.9 Pregnancy, childbirth and the puerperium
Infant	
Certain conditions originating in the perinatal period	Newborn affected by maternal factors and by complications of pregnancy, labour, and delivery P00-P96
Early neonatal death, SIDS	Ill-defined and unknown causes of mortality R95-R99.9
Congenital anomalies (CVS, CNS, other)	Congenital malformations, deformations and chromosomal abnormalities Q00-Q99.9
Infectious Diseases (pertussis, , etc.)	Certain infectious and parasitic diseases A00-B99
Meningitis	Meningitis due to other and unspecified causes G03 •arachnoiditis NOS •leptomeningitis NOS •meningitis NOS •pachymeningitis NOS
Encephalitis	Encephalitis, myelitis and encephalomyelitis G04 •acute ascending myelitis •meningoencephalitis •meningomyelitis
Lower respiratory (bronchiolitis, asthma, pneumonia, acute unspecified LRTI, bronchiectasis, Acute bronchitis, lung abscesses/pyothorax	Diseases of the respiratory system J00-J99
Neurological	Diseases of the nervous system G00-G99

[9] Information about stillbirths is recorded in the Mortality Collection. The Mortality Collection includes extra information about fetal and infant deaths, such as gestation and birth weight. The ICD codes we propose are: P95 Fetal death of unspecified cause Z37 Outcome of delivery, Z37.1Single stillbirth, Z37.3 Twins, one live born one stillborn, Z37.4 Twins, both stillborn, Z37.7 Other multiple births, all stillborn

Pregnancy duration will be classified using the gestational age field from the National Maternity Collection data set. This field gives the duration of pregnancy in number of completed weeks. Preterm will be defined as birth before 37 weeks gestation. Normal term will be defined as birth between 37 and 41 weeks gestation. Post-term will be defined as birth after 41 weeks gestation.

The following codes are available so we can get banded weeks of gestation.

1518 Duration of pregnancy

Code	Number	
O09.0	<5	Completed weeks
O09.1	5-13	Completed weeks
O09.2	14-19	Completed weeks
O09.3	20-25	Completed weeks
O09.4	26-33	Completed weeks
O09.5	34-36	Completed weeks
O09.9	Unspecified duration of pregnancy	

The yellow highlights are periods outside of the inclusion criteria.

Codes O09 should also have the following codes assigned for additional diagnoses:

Abortion	O00-007	Pregnancy with abortive outcome
Threatened abortion	O20.0	
Fetal death in utero	O36.4	
Premature rupture of membranes	O42	Before 37 completed weeks of gestation
Threatened premature labour	O47.0	False labour Before 37 completed weeks of gestation
Early onset of labour	O60	Early Preterm labour

Example

Patient admitted at 28 weeks gestation with a diagnosis of fetal death in utero (FDIU)

Medical and surgical induction of labour

O36.4	Maternal care for intrauterine death
O60.1	Preterm labour with preterm delivery
O09.4	Duration of pregnancy 26-33 weeks
Z37.1	Single stillbirth

1527- O48 will indicate prolonged pregnancy post dates and post term.

Some women deliver outside the hospital setting and this is estimated by the MoH at around 2%; however, information about these births is available via the National Maternity

Collection. All births, regardless of delivery setting, are assigned a unique National Health Index number. This allows capture of all post-birth hospital and/or notification events for all infants.

Inclusion criteria

Women

NZ women who are pregnant during the study period

Infants

Infants of the women who were pregnant during the study period

Study Two: Prospective intensive monitoring study of safety in pregnant women administered Tdap vaccination

This is a prospective observational study. It will describe any adverse events in pregnant mothers who received Tdap occurring within one month following immunisation. The data for this part of the study will be collected using the same methodology as that currently being used in Canterbury (i.e., Study Three currently in progress) and will therefore be directly comparable and also joint analysis will be possible for the maternal outcomes.

NOTE: We will not have any cases of spontaneous abortion in Studies Two and Three as the lower gestation eligible for vaccination and therefore inclusion in the study is 28 weeks.

Study population

All women vaccinated during pregnancy at any General Practice in NZ with Tdap vaccine will form the Study Two population.

Study participants

Study Two will include women 28–38 weeks pregnant.

Women presenting to participating general practices for pertussis vaccine. Practice nurses will be asked to inform all eligible women presenting about the study and with their consent provide their contact details to the research team. Recruitment will continue until the required numbers are achieved at which time practices will be asked to cease recruiting or modify their eligibility criteria.

Practices will be asked to document the following information for women who decline to participate. To identify possible biases between practice and pregnant women who chose to participate versus decliners coded reasons for decline (i.e., too busy, dislike being involved in research), age band, ethnicity and parity will be collected by the recruiting practice nurses. Information will also be collected on the practices that have a higher decline rate. This will include the geographical location, overall socioeconomic band of the practice population and ethnicity mix.

Practice nurses will invite women to be contacted by the study team. Contact details will be obtained from their General Practice only for women who have verbally consented to be contacted. Potential study participants will be identified by fax receipt of a consent to follow up from the General Practice to the investigators. Practices will be provided with a gift voucher for each participant to acknowledge their time.

It is possible that a small percentage of women may have received Tdap from sources other than their GP (e.g., healthcare workers or women who are seen at hospital with wounds that require a tetanus booster). However it is anticipated this will only be a very small proportion as most Emergency Departments and Accident and Emergency Centres in NZ only stock

ADT, not Tdap. Furthermore the records of claims through Ministry will accurately reflect the total number of women in NZ receiving Tdap during pregnancy.

Inclusion criteria for Study Two

Women

Pregnant women who have received the Tdap vaccine during pregnancy between 28 and 38 weeks of gestation.

Compliant with routine antenatal care, including at least one ultrasound early in pregnancy.

Have associated information on the specific vaccines given, including batch number.

Exclusion criteria for Study Two

If a woman has already had her baby prior to being contacted by the study team she will not be enrolled in the study.

Endpoints for Study Two

Rates and patterns of adverse events in women who were administered Tdap during pregnancy

Multiple pregnancies

While the number of visits during pregnancy could have an impact on the pregnancy outcome within the study population in Study Two and Three (but not in Study One). The frequency of prenatal care is a potential confounder as it may be associated both with women receiving TdaP or not, and with birth outcomes. There is no way to capture the number of prenatal visits women have from nationally available data. However, the National Maternity Collection does "contain data on primary maternity services provided under Section 88 of the NZ Public Health and Disability Act 2000. This information is sourced from lead maternity carer claims for payment." This information might be useable as a proxy to indicate frequency of prenatal care.

Study Three: Intensive monitoring study of pregnant women administered Tdap during pregnancy and their infants

Study Three involves extending and supporting the intensive monitoring study currently being conducted in the Canterbury DHB by Dr Tony Walls (Principal Investigator). Briefly this study runs as per Study Two except the women and their infants are followed up intensively for a period of one year after the birth of the infant. The data collected for the period of one month post vaccination in Study Three will be able to be pooled for the overlapping subset of participants also in Study Two.

Study Three includes women receiving the vaccine under the DHB programme at 30–36 weeks in the Canterbury region.

Figure 1. Study population and outcomes

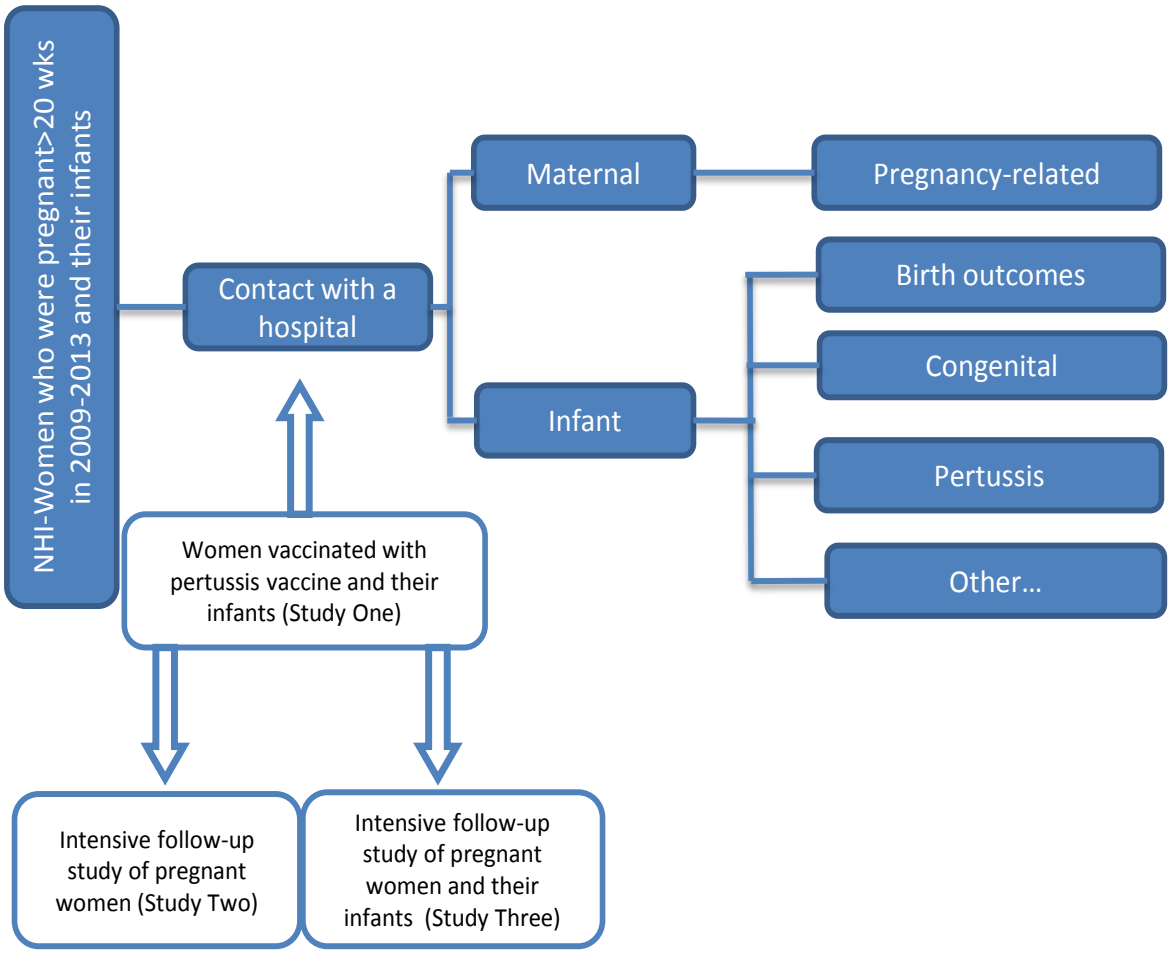
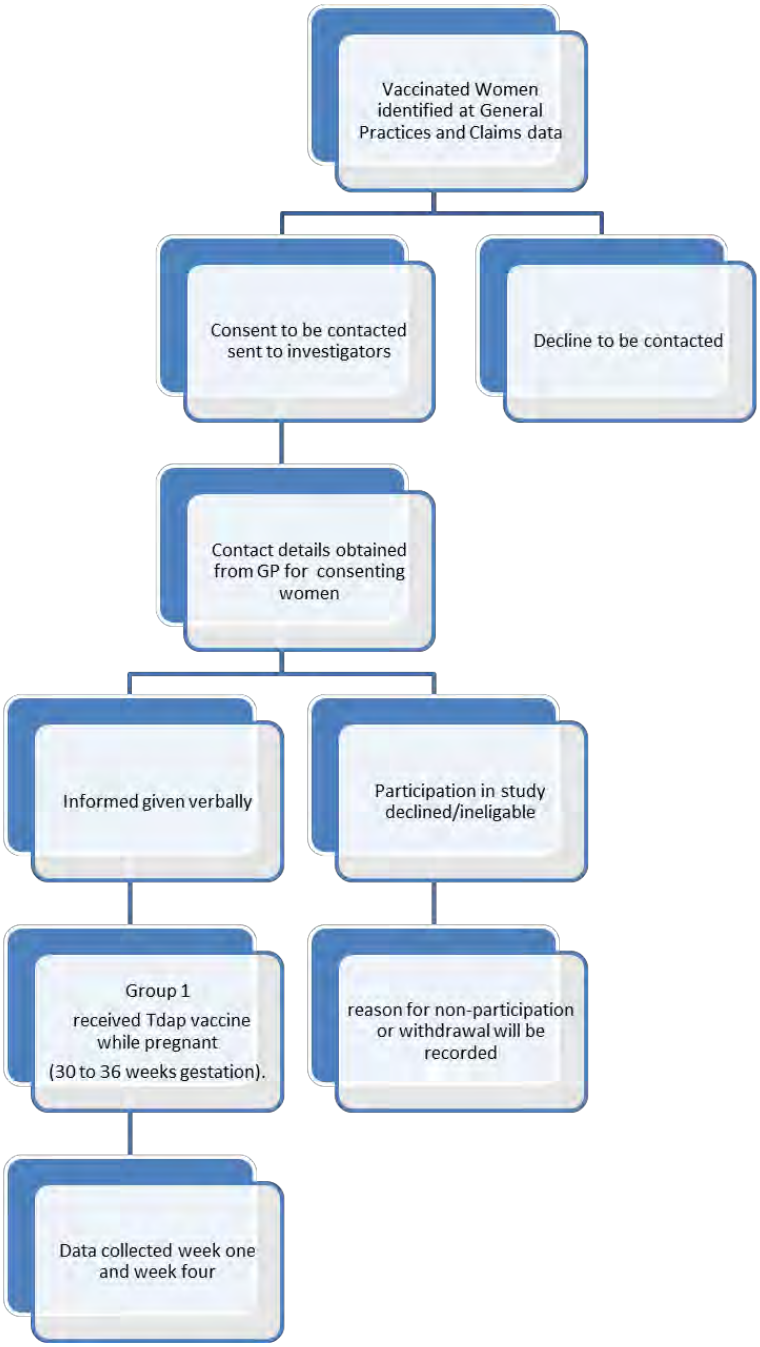


Figure 2. Monitoring of pregnant women receiving pertussis during pregnancy



Canterbury DHB continues intensive follow up for birth outcomes and infant outcomes for one year for a sample of 300 women and their infants. Infant follow up at three to seven months and 12 months of age in this DHB as per Canterbury protocol (Study Three) (*Appendix 8)*.

Study procedures

Study One (utilising whole population data-linking)

Data sets for hospitalisations, pertussis notifications, infant vaccination and maternal Tdap vaccination will be obtained for the period 1 January 2009 to year ending 2013 from the following national databases:

- National Minimum Dataset for hospitalisation data
- The National Immunisation Register for infant immunisation data
- Notification data from the ESR
- Pregnancy Immunisation records from the HealthPAC claims database
- National Maternity Collection.

Data cleansing and data matching will progress for the first half of 2014.

Analysis will be carried out during the second half of 2014.

Study Two (intensive monitoring study of pregnant women)

Year 1: 2013

Enrolment

Practice staff will identify potential participants based on eligibility criteria (*Appendix 1*), provide them with an information sheet summary (*Appendix 2*) and with their consent, complete and fax a referral form (*Appendix 3*) to the research team. Practice staff will provide women consenting to be contacted by the research team with a full participant information sheet (PIS) (*Appendix 5)* to take home. A member of the research team will make the first contact with mother by phone as soon as possible after identification to:

provide further information about study and obtain verbal informed consent for participation (written consent form sent out following verbal consent given by phone, *Appendix 4*)
capture any solicited events within first 48 hours and first 7 days of receiving vaccine(s)[10] (*Appendix 6).*

Contact General Practice once consent obtained for cross checking recorded DOB, ethnicity, NHI, due date and vaccination history details.

Four weeks post-vaccine administration to pregnant woman (prospective)

Phone interview *(Appendix 7)* to capture any solicited events in mother up to four weeks after receipt of vaccine. Any events requiring General Practice consultation will be verified by the practice.

End of data collection: Provide voucher to mother to acknowledge time contribution.

Canterbury DHB – additional data.

(See Canterbury DHB study protocol for additional data on infant outcomes [*Appendix 8*])

Informed consent:

An additional consent form *(*included in Appendix 8) will be used to obtain signed informed consent for participation and handling of personally identifiable information and safety data.

[10] For cases contacted retrospectively we will rely on patient recall of events.

If a woman chooses not to participate or to withdraw from the study at a later date the reason for non-participation or withdrawal will be recorded when given.

Confidentiality:

Data will be collected and stored on a password protected database located in the Immunisation Advisory Centre, University of Auckland. The National Health Index (NHI) number will be used during data collection to identify study participants alongside a study identification number. The study identification number will not include any details that could potentially identify the study participant (i.e., date of birth). The NHI is included because it will provide the easiest access to information from GP records.

Prior to any data analysis the NHI will be removed from the database and a study identification number assigned.

Study Three (intensive monitoring study of pregnant women and their infants)

Year two: 2014

The additional data collected in Canterbury will run over year two. (See protocol for Canterbury study, [*Appendix 8*]. Appendices referred to in the table below are included within the Canterbury protocol). Study assessments and procedures are summarised in the table below. The outcomes in infants are collected in the Canterbury DHB only as part of a pre-existing study.

Scheduled assessments	Adverse events in mother	Outcomes for infant	Both mother and baby
At enrolment	[1]**First contact with mother by phone** (standard script) as soon as possible after identification to: provide information about study and obtain detailed informed consent for participation (written consent form sent out if verbal consent given by phone) capture any solicited adverse events within first 48 hours and first 7 days of receiving vaccine (s) Contact General Practice once consent obtained to obtain details of vaccination *(Appendix 3)*		Contact with mother monthly either by phone or e-mail[4]. If infant has symptoms* consistent with pertussis or a significant contact** with proven case will be invited for clinical review by study team Paediatrician.
4 weeks since vaccine administration	[2]**Written questionnaire** *(Appendix 5)* to capture any solicited adverse events in mother up to 4 weeks after receipt of vaccine		

6-week check	**Written questionnaire** (*Appendix 6*) administered by telephone to GP to determine pregnancy outcome and medically attended adverse events in mother since last contact.	**Written questionnaire** (*Appendix 6*) administered by telephone to GP practice to capture birth history, weight and head circumference, any congenital abnormalities, neonatal death (<29 days) Details of 6-week check and confirm receipt of 6-week vaccination. Document any prior GP or hospital visits.	If an unsolicited adverse event is noted during these calls, it will follow the same safety reporting procedures as other AEs in the study.
3–6 month check		Weight, head circumference, vaccination status, and standardised clinical examination by Plunket Nurse as recorded in Well Child book *(Appendix 6)*.[3]	
1-year follow-up		Final contact with mother about pertussis exposure and/or symptoms. Vaccination status – if not completed infant vaccinations by 6 months.	

1 Three attempts will be made to contact mother by telephone within 1 week of notification of receipt of Tdap. If an e-mail address is available this will also be used if telephone contact is unsuccessful.
2 Written questionnaire will be sent to mother before 4 weeks have elapsed since receipt of vaccine. Telephone contact will be made at 4 weeks of receipt of vaccine and two further times if the completed questionnaire has not been received within 1 week.
3 Mothers will be encouraged to attend Plunket for check ups during the first 6 months. If there is no available recorded weight and head circumference between 3-6 months of age this will be done by a member of the study team. The mother will be contacted three times via email or phone to get this information.
4 Three attempts will be made by phone or email to contact the mother each month
*Persistent cough lasting for >10 days and/or post-tussive vomiting
** Close contact defined as being in the same room as the person for > 1 hour or 5 minutes of face to face contact with a person with proven pertussis who was symptomatic.

Data management/Data confidentiality

Data will be managed and protected according to the requirements of the Ethical approval. An Access database will be developed to receive the data reported on the survey forms (Study Two and Three).

Data set fields will be identified

Code tables will be created

Vaccinee data verified as non-duplicated, then NHI number, name and phone number will be replaced by a sequential number (These are the only variables that contain personal identifiable information and will also be used to ensure there is no duplication of survey and extraction of maternal and pregnancy data at the end of the study).

Data set validation

Data set will be double entered for validation
Any corrections will be reviewed by a third party

Data confidentiality

No names or NHI numbers will be published
Visibility of the National Health Index number (NHI) of the participant's records will be password protected and restricted to the key investigators before being removed at the end of the study.
Access to complete data sets will be limited to the investigators and data analysts.

Data storage

The datasets will be stored in a password-protected file within The University of Auckland and the physical files will be held in a locked filing cabinet by the Principal Investigator/s Dr Helen Petousis-Harris who will store it for 10 years in accordance with the NZ ethical guidelines.

Study duration

	Intensive study	Population datalink study
Month one	First participants enrolled in intensive study	
Month six	Last participants enrolled in intensive study (this potentially may be extended depending on enrolment	Preparation for population data collection. Obtain ethical approval
Month 12	Interim report due	Receive 2009-2013 data, commence data cleansing and data matching
Month 18	Last of the 1 year follow up data will be collected	Commence analysis
Month 20	Final study report due	
Month 22	Submission of publication	
Month 24		Final report
Month 28		Submission of publication

Statistical analysis and sample size justification

Study One (N=~325,000)

Sample size:

Over the five-year period of this study there will be approximately 325,000 births. The percentage vaccinated will increase over the time period as the funded vaccine is promoted over the epidemic but on average approximately 30% of mothers would be expected to have received vaccination during pregnancy.

Analysis:

Logistic regression will be used to estimate odds ratios for the risk for (specific) adverse events for both mothers and infants in vaccine exposed and unexposed groups. Age, ethnicity and socioeconomic deprivation and season for hospital admission will be included as additional explanatory variables.

As specific diagnoses are not necessarily independent events each person will only be counted once for each hospitalisation, the primary diagnosis and repeat admissions for the same episode will be removed, including transfers from one hospital to another.

For diagnosis where individuals may have multiple admissions for different occurrences and the outcome is a count, Poisson regression will be used with testing and adjustment for overdispersion where required.

The temporal relationship between onset of events and vaccination will be presented including distribution where appropriate,

Serious adverse events will be reported as detailed clinical cases.

To analyse the effect of TdaP on still births we will perform a survival analysis. The time dependent explanatory variable of vaccination status and 'failure' of still birth and censored at birth, also including demographics as explanatory variables. The independent explanatory variable will be TdaP vaccination status of the mother (time dependent). Time will commence at the beginning of the inclusion time for an individual— 28(20) weeks gestation. Women will be censored at time of live birth or at the end of the study period, 31 December 2013, whichever occurs first.

Study Two (N=~300)

Estimated number of women receiving pertussis vaccine during pregnancy for study period, potential study population

The birth cohort in NZ is approximately 65,000 per annum. Tdap is funded for pregnant women, but it is difficult to estimate how many women will take up the vaccine. In one DHB with a birth cohort of 6,000 who were first to offer pertussis vaccine free to pregnant women, 220 claims for the Tdap vaccine had been lodged in six weeks and 1,164 over eight months. At the 10th June 2012, out of 255 claims processed at that time 22 (9%) of women had not consented to follow up. The number of women able to be recruited to the Canterbury study is limited by available nurse time.

Based on the experience in Canterbury assuming sufficient workforce capacity the potential number of women available for follow up over a one-year period is:

National birth cohort 65,000
Uptake of pertussis vaccine in pregnancy 10–40%
Potential annual vaccinated cohort 6,500–26,000

Likely to consent (90%) 5,850–23,400
Eligible to participate (87%) 5,090–22,620

- Participation by general practices (success in obtaining informed consent to follow up) estimate 30–90% (likely to be higher rather than lower)
- Estimated minimum and maximum number of women for follow up of pertussis vaccine 1,527–20,358

Sample size and power

As this is an observational study we plan to describe the confidence intervals for the proportions of AEs. With a sample of 300 vaccinated participants, if event occurs in 10% of the group the 95% CI would be 7–14%; if 5%, 2.8–8.1%; if 1%, 0.2–2.9%. Additional power will be achieved by combining the data from the Canterbury study (Study Three), which aims to include 300 women vaccinated with Tdap.

Statistical Analyses

The pregnancy safety data will be descriptive in nature, including percentages and 95% confidence intervals. The rates of AEs and SAEs following pertussis vaccine will be discussed in context with the rates previously described for pertussis. The expected background rates of MAEs and SAEs for Tdap given during pregnancy are unknown, but as a guide the rates of MAEs for pregnant women receiving influenza vaccine previously reported ranged from 1.1 to 3.8% while the rate of SAEs ranged from 0.4 to 1.5%.

Women who have complicated pregnancies will be excluded from the final analyses and described separately.

The temporal relationship between onset of events and vaccination will be presented including distribution where appropriate.

Serious adverse events will be reported as detailed clinical cases. Other events will be groups according to Brighton Collaboration Definitions.

Study Three (N=~300)

From the protocol for Canterbury DHB (Appendix 8)*: Principal Investigator, Tony Wall.*

As this study is an observational study, the pregnancy outcomes and safety data will be descriptive in nature. The rates of AEs and SAEs will be compared to published background rates for the general population. The expected rates of MAEs and SAEs for Tdap given during pregnancy is unknown, but as a guide the rates of MAEs for pregnant women receiving influenza vaccine in this paper ranged from 1.1 to 3.8% while the rate of SAEs ranged from 0.4 to 1.5%. Where the known background incidence of 0.01 for a particular adverse event, a sample size of 300 achieves 80% power to detect an additional incidence rate of 0.0175 when the significance level is 0.05.

It is anticipated that the difference in AEs between subgroups in the trial will be small. As this is an observational study we therefore plan to describe the confidence intervals for the proportions of AEs within each group. A sample size of 300 produces a two-sided 95% confidence interval with a width equal to 0.081 when the sample proportion is 0.150.

Women who have multiple pregnancies and/or complicated pregnancies will be excluded from the final analyses and described separately.

Total expected participants

	Study population	Sample size	

Study One	325,000		Total pertussis-vaccinated maternal population
Study Two	1,527–20,358	300	~300 pertussis vaccinees
Study Three	6,000	300	300 pertussis vaccinees

Vaccines

Pertussis vaccine

The pertussis vaccine funded for pregnant women is Boostrix®. There are other licensed vaccines but no other pertussis vaccines currently funded for pregnant women in NZ.

Specific vaccine supply requirement

N/A. This is an observational study. There are no vaccine requirements for this study.

Adverse experience reporting

Adverse Event data are being accessed/collected during this project in Study Two and Three.

The Investigator will report SAEs (either initial of follow-up reports) to:

The NZ Centre for Adverse Reaction Monitoring (CARM) at the University of Otago according to local requirements. (See Appendix 9, contract Exhibit D, CARM Reporting Form)
The Ethics Committee according to requirements
The Marketing Authorisation Holder within 24 hours according to contracted safety reporting requirements defined in the study contract. Case reporting will include the relevant variables in the GSK "with intensity GCSP reporting form". (See Appendix 10)

Administration during pregnancy is relevant in the age group, so pregnancy reporting is expected to be relevant. All participants will be pregnant.

There will be no causality assessments conducted during this study as this is observational and there is no intervention.

Any adverse events that are reported to the NZ Centre for Adverse Reaction Monitoring (CARM) undergo causality assessment. This data is provided to the WHO and the MoH.

CARM is the official regulatory body in charge of receiving all adverse event reports in NZ. CARM collaborates with and pools anonymised data, together with other national monitoring centres, into the database of the World Health Organization's International Drug Monitoring Programme.

Serious adverse events—Study One

There will be no individual case adverse event reporting for Study One, which is a retrospective study using data linkage.

Serious adverse events—Study Two

This study is following women for four weeks following vaccination. Should there be any cases of stillbirth, fetal death, spontaneous abortion, elective abortion or other significant pregnancy outcomes during the period of active data collection, that we become aware of, these will be reported within 24 hours.

Reporting will occur on pregnancy outcomes, fetal outcomes and neonatal status at the end of the study for the Study One participants.

There will be no causality assessment performed as the study staff will not be able to do this based on telephone interviews. However causality process is undertaken via the established NZ CARM process.

The investigators and study team will be clearly informed and reminded of the importance of this timely reporting of any SAE to CARM.

Serious adverse events—Study Three

This study is following women for 12 months following vaccination. Should there be any cases of stillbirth, fetal death, spontaneous abortion, elective abortion or other pregnancy outcomes during the period of active data collection these will be reported within 24 hours of notification.

There will be no causality assessment performed as the study nurses will not be able to do this based on telephone interviews.

The investigators and study nurses will be clearly informed and reminded of the importance of this timely reporting of any SAE to CARM.

Data sharing with OCEANS database

We intend to enable data sharing for Study Two and Three with the OCEANS database. We await information from GSK on the database requirements. Data sharing of de-identified information will enable rapid transfer of information on both serious and **non-serious adverse events**. The data sharing will be covered in the Ethical approval and in the patient informed consent.

The data to GSK will be provided in MS Excel format. All variables collected in Study 2 and 3 will be provided in this file.

Other adverse event reporting:

Adverse events not meeting criteria for an SAE that are subject to clinician verification/review will be reported to CARM according to local requirements at the discretion of the clinician/investigator.

The Investigators shall report all clinical safety data defined below. In addition, the investigators will report any other clinical safety data arising during the study at such times as GSK may require.

Definition—SAE

A SAE is any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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.

c) Requires hospitalisation or prolongation of existing hospitalisation

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

AE definitions

An AE is any untoward medical occurrence in a patient or clinical investigation subject or consumer, temporally associated with the use of a product, whether or not considered related to the product.

Examples of an AE include:

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
Signs, symptoms, or the clinical sequelae of a suspected interaction
Signs, symptoms, or the clinical sequelae of a suspected overdose

Examples of an AE do not include a/an:

Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

All as per Brighton Collaboration where these definitions are available.

Definitions for local reactions and fever	
Local Reactions	Systemic Events
Level one diagnostic certainty is: Any description of morphological or physiological change at or near the injection site that is described or identified by a health care provider Level two diagnostic certainty is: Any description of morphological of physiological change at or near the injection site that is described or identified by another person **Categories for event classification** Level 1: as specified in the case definition for a local reaction Level 2: as specified in the case definition for local reaction Insufficient evidence for a local reaction Not a case of a local reaction **Interval for onset of local reaction or first observation** >0-24 h 25-48 h 49-72h 73h – 7 days >7 days Include numbers of subjects with local reactions newly present at each specified time as %. **Diameter of the local reaction** >0.0 - <1.0 cm ≥1.0 – 2.5 cm	**Fever** Endogenous elevation of at least one measured body temperature of ≥38°C Time intervals 0 – 24hr Day 1 0 – 24hr Day 2 Day 3-7... Increments <38°C 38.0-38.4°C 38.5-38.9°C Etc.... >41°C

≥2.5 – 5.0 cm ≥5.0 - <10.0 cm ≥10.0 - <15.0 cm ≥15.0 - <20.0cm ≥20.0 - <30.0 cm ≥30.0 cm Pain scale to include measure of functionality 0 = No pain 1 = Mild, still able to move arm normally 2 = Moderate, hurts to move arm normally or to touch 3 = Severe, unable to move arm	

Ethical considerations

Ethical approval for this study will be obtained from the NZ Ministry of Health and Disability Ethics Committee. These guidelines are based on statements from NZ and international guidelines, including the World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects (WMA 2008) and the Council for International Organizations of Medical Sciences' International Guidelines for Ethical Review of Epidemiological Studies (CIOMS 1991).

Details about the National Ethics Advisory Committee and the Ethical Guidelines for Observational Studies can be accessed http://neac.health.govt.nz/streamlined-ethical-guidelines-health-and-disability-research

Whilst we are not undertaking any clinical work (there is no intervention, only observation), we will be observing the standards required by the national ethics committee and GCP standards, in which our team are familiar.

We intend acknowledging participating practices for their nursing time taken in identifying participants and assisting in recruitment and acknowledging patient participants for their time taken to respond to interviews. Reimbursement will be in the form of retail vouchers: the amount of which the practice receives will be determined by the time and effort provided to recruit our study participants. Patient participants will each receive a $40 supermarket or petrol voucher. This is line with acceptable NZ practice for reimbursement but dependent on approval from the ethics committee.

Protocol registration

A Universal Trial Number (UTN) has been allocated by the World Health Organization specifically for Studies One and Two (U1111-1148-0718). These studies were subsequently registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) and allocated the ACTRN: ACTRN12613001045707.

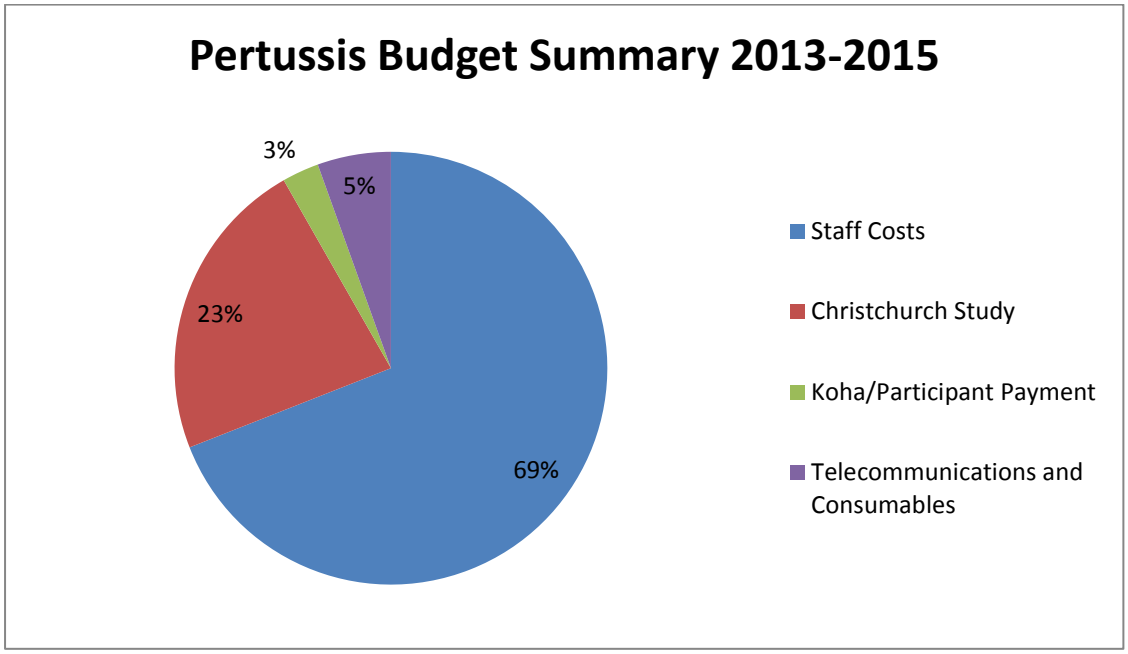
Dissemination of results

Results will be disseminated via the following mechanisms:

Report and presentation to the funder
Report and presentation to the NZ MoH and Pharmac
Presentations considered for ESPID or other appropriate infectious disease and vaccine and vaccination conferences
Publication/s in international pertinent journal such as *Vaccine* or *Paediatrics*

Itemised Study Budget

See detailed budget in separate spreadsheet.



Pertussis Budget Summary 2013-2015	Total Cost (NZD)	Percentage of Total Cost	Comments
Staff Costs	$600,800	69%	Academics, Project Manager, Research Nurse and Data Analyst
Christchurch Study	$197,700	23%	Dr Tony Wall, Research Nurse and Participant Payments
Koha/Participant Payment	$24,000	3%	Payment to participants and participating GP practices
Telecommunications and Consumables	$47,800	5%	Telephones, Office Costs, Data Extraction
TOTAL COST	**$870,300**	**100%**	

Curriculum vitae

New Zealand MSI Curriculum Vitae Template

PART 1

1a. Personal details				
Full name	*Title* Dr	*First name* *Helen*	*Second name(s)* *Aspasia*	*Family name* *Petousis-Harris*
Present position	Senior Lecturer, Dept. General Practice and Primary Health Care Director of Research, Immunisation Advisory Centre			
Organisation/Employer	University of Auckland/ UniServices			
Contact Address	Level 3, Building 734, Tamaki Innovation Campus			
	Morrin Rd, Glen Innes			
	Auckland		**Post code**	
Work telephone	9232078	**Mobile**	0274716749	
Email	h.petousis-harris@auckland.ac.nz			
Personal website (if applicable)	http://immune.org.nz			

1b. Academic qualifications

2012	PhD	Vaccinology	University of Auckland
2006	PGDipSc (Distinction)	Molecular Medicine	University of Auckland
1998	BSc	Biological Science	University of Auckland
2008	Diploma	Advanced Vaccinology	University of Geneva and Foundation Merieux

1c. Professional positions held

2012 – Current	Director, Immunisation Research and Vaccinology, Immunisation Advisory Centre, University of Auckland

2008 – 2011	University of Auckland Researcher, Director of Research, Immunisation Advisory Centre
2007 – Current	Senior Lecturer, Department of General Practice and Primary Health Care, University of Auckland
2002 – 2004	University of Auckland, Honorary Assistant Research Fellow
1998 – 2002	University of Auckland, Researcher, Immunisation Advisory Centre

1d. Present research/professional speciality

Fifteen years immunisation research experience in New Zealand including clinical research, social science, epidemiological and health systems research. Media spokesperson on vaccines and vaccination. Primary role within the Immunisation Advisory Centre is to provide evidence based information on vaccines and vaccines to inform current national practice. Teaching in both postgraduate and under graduate courses including course convener of postgraduate Vaccinology paper. Teaching for health professionals delivering immunisation.

1e. Total years research experience	15 years

1f. Professional distinctions and memberships (including honours, prizes, scholarships, boards or governance roles, etc)

2008	Award for Best Academic Presentation, New Zealand Annual General Practice Research Retreat
2007	Academic General Practice Research Award. RNZCGP
2004	Academic General Practice Research Award. RNZCGP
2001	Royal Society of New Zealand Science Communication Fellowships
2010 - current	Professional Member Royal Society of New Zealand (MRSNZ)

Invited Plenary

Safety Issues and Influenza Vaccines: Febrile events following administration of 2010 seasonal influenza vaccine. Global Collaborative Network for Vaccine Safety Studies. Les Pensieres, Fondation Merieux Conference Centre, Veyrier-du-Lac, Annecy. France. March 28-30 2011.

1g. Total number of *peer reviewed* publications and patents	Journal articles	Books, book chapters, books edited	Conference proceedings	Patents
	32	2	26 (last 5 years)	

PART 2

2a. Research publications and dissemination

Peer-reviewed journal articles

PETOUSIS-HARRIS H. Pneumococcal disease in New Zealand and prevailing inequalities, the tip of the lower respiratory infection iceberg. Editorial. New Zealand Medical Journal. 2013. 126;1378:9-11

PETOUSIS-HARRIS H, POOLE T, STEWART J, TURNER N, GOODYEAR-SMITH F, COSTER G, ET AL. An investigation of three injections techniques in reducing local injection pain with a human papillomavirus vaccine: a randomized trial. Vaccine 2013 Feb 6;31(8):1157-62.

POOLE T, GOODYEAR-SMITH F, **PETOUSIS-HARRIS H**, DESMOND N, EXETER D, POINTON L, ET AL. Human papillomavirus vaccination in Auckland: reducing ethnic and socioeconomic inequities. Vaccine 2012 Dec 17;31(1):84-8.

MUELLER S, EXETER DJ, BUCK CD, O'SULLIVAN D, **PETOUSIS-HARRIS H**, TURNER N. Measuring Disparities in Immunisation Coverage among Children in New Zealand. Health and Place. *18(6):1217-1223*.

PETOUSIS-HARRIS H, POOLE T, TURNER N, REYNOLDS G. Febrile events including convulsions following the administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children: The importance of routine active safety surveillance. Vaccine 2012;30:4945-52.

GOODYEAR-SMITH F, GRANT C, POOLE T, **PETOUSIS-HARRIS H**, TURNER N, PERERA R, ET AL. Early connections: effectiveness of a pre-call intervention to improve immunisation coverage and timeliness. J Prim Health Care 2012;4(3):189-98.

PETOUSIS-HARRIS H, GRANT C, GOODYEAR-SMITH F, TURNER N, YORK D, JONES R, STEWART J. What contributes to delays? The primary care determinants of immunisation timeliness in New Zealand. Journal of Primary Health Care 2012;4(1):12-20

PETOUSIS-HARRIS H. Saturated fat has been unfairly demonised: Yes. Journal of Primary Health Care 2011;3(4):317-9.

PETOUSIS-HARRIS H, POOLE T, BOOY R, TURNER N. Fever following administration of two inactivated influenza vaccines--A survey of parents of New Zealand infants and children 5 years of age and under. *Vaccine 29:2933-2937,* 2011.

DESMOND N, GRANT C, TURNER N, **PETOUSIS-HARRIS H**, GOODYEAR-SMITH F. Who makes a difference? The nurse factor in immunization coverage. *Australian Journal of Advanced Nursing. 29;1,* 2011

GRANT, C. C., **PETOUSIS-HARRIS**, H., TURNER, N., KERSE, N., GOODYEAR-SMITH, F. A., JONES, R., STEWART, J. (2011). Primary care practice and health professional determinants of immunisation coverage. Journal of Paediatrics and Child Health, 47(8), 541-549.

PETOUSIS-HARRIS H, GOODYEAR-SMITH F, KAMESHEWAR K, TURNER N. Fact or fallacy? Immunisation arguments in the print media. *Australian and New Zealand Journal of Public Health. 34;5:521-526*, 2010.

GRANT CC, TURNER NM, YORK DG, GOODYEAR-SMITH F, **PETOUSIS-HARRIS HA**. Factors associated with immunisation coverage and timeliness in New Zealand. *British Journal of General Practice; 60:e113-e20*, 2010

PETOUSIS-HARRIS H, TURNER N. Examining Immunisation in New Zealand. *Vaccines in Practice;2(4):10-1,* 2009

TURNER N, ROUSE P, AIREY S, **PETOUSIS-HARRIS H**. The cost of immunising at the general practice level. *Journal of Primary Health Care*;*1(4):286-95,* 2009

TURNER N, GRANT C, GOODYEAR-SMITH F, **PETOUSIS-HARRIS H**, et al. Seize the moments: missed opportunities to immunize at the family practice level. *Family Practice 26(4):275-8,* 2009

GOODYEAR-SMITH F, YORK D, **PETOUSIS-HARRIS H**, TURNER N, COPP J, KERSE N, et al. Recruitment of practices in primary care research: the long and the short of it. *Family Practice 26(2):128-36,* 2009

GOODYEAR-SMITH F, GRANT C, **PETOUSIS-HARRIS H**, TURNER N, et al. Immunization champions: characteristics of general practitioners associated with better immunization delivery. *Human Vaccines;5(6):403-11*, 2009

GOODYEAR-SMITH F, GRANT C, YORK D, KENEALY T, COPP J, **PETOUSIS-HARRIS H**, et al. Determining immunisation coverage rates in primary health care practices: a simple goal but a complex task. *International Journal of Medical* Informatics l;77(7):477-85, 2008.

PETOUSIS-HARRIS H. Vaccine injection technique and reactogenicity--evidence for practice. *Vaccine 25;26(50):6299-304*, 2008

PETOUSIS-HARRIS H, GOODYEAR-SMITH F, SOE B, TURNER N. Family practice nurses perspectives on barriers to childhood immunisation. *Vaccine;23:2725-2730,* 2005

PETOUSIS-HARRIS H, GOODYEAR-SMITH F, RAM S, TURNER N. The New Zealand national immunisation hotline - what are callers seeking? *Vaccine*;23:5038-5044, 2005

GOODYEAR-SMITH, F., **H. PETOUSIS-HARRIS**, et al. "The complex nature of improving immunisation rates: perceived barriers to uptake facing general practitioners and practice nurses." New Zealand Family Physician.

GOODYEAR-SMITH F, **PETOUSIS-HARRIS H**, SOE B, TURNER N. Comparison of general practitioner and practice nurse perceived barriers to immunisation uptake. *New Zealand Family Physician;32(3):164-171,* 2005

GOODYEAR-SMITH F, WONG F, **PETOUSIS-HARRIS H**, WILSON E, TURNER N. Follow-up of MMR Vaccination Status in Children Referred to a Pediatric Immunization Clinic on Account of Egg Allergy. *Human* Vaccines;1(3):25-29, 2005

PETOUSIS-HARRIS H, GOODYEAR-SMITH F, GODINET S, TURNER N. Barriers to Childhood Immunisation among New Zealand Mothers. *New Zealand Family Physician*;*29:396-401*, 2002

PETOUSIS-HARRIS H, TURNER N, KERSE N. New Zealand Mothers' Knowledge of and Attitudes towards Immunisation. *New Zealand Family* Physician;29:4:240-46, 2002

PETOUSIS-HARRIS H, BOYD E, TURNER N. Immunisation education in the antenatal period. *New Zealand Family* Physician;31:303-06, 2004

PETOUSIS-HARRIS H, GOODYEAR-SMITH F, TURNER N, SOE B. Family physician perspectives on barriers to childhood immunisation. *Vaccine;22(17-18):2340-44*, 2004

PETOUSIS-HARRIS H, TURNER N, SOE B. Parent views on school based immunisation: A survey of parents of year 1 and 6 children in three diverse Auckland schools. *New Zealand Family Physician*;*31:222-28*, 2004

Peer reviewed books, book chapters, books edited

GOODYEAR-SMITH F, **PETOUSIS-HARRIS H**. Immunization Scares in the Media. in The Sky is Falling. Robert Bartholemew. Editor. 2011

PETOUSIS-HARRIS H. Factors associated with vaccine reactogenicity in school aged children and young adults following administration of two protein-based vaccines [PhD]. Auckland: University of Auckland; 2012.

Refereed conference proceedings

PETOUSIS-HARRIS H, POOLE T, REYNOLDS G, TURNER N. Fever and febrile convulsions following influenza vaccine - importance of routine safety surveillance. In: Public Health Association of

Australia, editor. 13th Australian National Immunisation Conference. Darwin, 2012.

PETOUSIS-HARRIS H, POOLE T, STEWART J, TURNER N, GOODYEAR-SMITH F, LENNON D. What is the optimal injection technique for administering HPV vaccine? In: Public Health Association of Australia, editor. 13th Australian National Immunisation Conference. Darwin, 2012.

EXETER, D., MUELLER, S., **PETOUSIS-HARRIS**, H. A., & TURNER, N. (2011). Immunization coverage disparities in New Zealand: a geographical perspective. In 14th International Medical Geography Symposium. Durham, UK.

EXETER, D., MUELLER, S., BUELL, H. E., **PETOUSIS-HARRIS, H. A**., & POOLE, T. (2011). The association between immunisation coverage and vaccine preventable diseases in New Zealand. In 14th International Medical Geography Symposium. Durham, UK.

PETOUSIS-HARRIS H, POOLE T, REYNOLDS G, TURNER N. Fever and febrile seizures in New Zealand children following administration of 2010 (H1N1-containing) inactivated influenza vaccines - findings and lessons. 2011 New Zealand Immunisation Conference. Rotorua, New Zealand, 2011.

PETOUSIS-HARRIS H, POOLE T, STEWART J, TURNER N, LENNON D, COSTER G, et al. Intramuscular injection technique - what matters and how much? Findings from the FAR trial. 2011 New Zealand Immunisation Conference. Rotorua, New Zealand, 2011.

FELICITY GOODYEAR SMITH, **HELEN PETOUSIS-HARRIS**, TRACEY POOLE et al. Early Connections: Improving immunisation coverage and timeliness. The 2011 New Zealand Immunisation Conference. Novotel Hotel. Rotorua. 2011

PETOUSIS-HARRIS H, GOODYEAR-SMITH F, KAMESHWA K, TURNER N. Vaccination and the media: A match made in hell? New Zealand Immunisation Conference: University of Auckland, Auckland, 2009.

PETOUSIS-HARRIS H. Factors associated with reactogenicity following administration of an OMV Meningococcal Vaccine in children aged 8 – 12 years. New Zealand Immunisation Conference: University of Auckland, Auckland, 2009.

GOODYEAR-SMITH FA, GRANT CC, TURNER NM, **PETOUSIS-HARRIS HA**, DESMOND NM. Core components that determine complete & timely immunization of children in family practice. North American Primary Care Research Group (NAPCRG) 36th Annual Meeting, Puerto Rico, 15 Nov 2008 - 19 Nov 2008. 2008

PETOUSIS-HARRIS HA, GOODYEAR-SMITH FA, KAMESHWAR K, TURNER NM. Immunisation and the media: a match made in hell? RNZCGP Conference, Queenstown, New Zealand, 17 Jul 2008 - 18 Jul 2008. 2008

PETOUSIS-HARRIS H, GOODYEAR-SMITH F, KAMESHWA K, TURNER N. Vaccination and the media: A match made in hell? Public Health Association of Australia 11th National Immunisation Conference Immunisation: Old challenges and new frontiers. Surfers Paradise Marriott Gold Coast, 2008.

PETOUSIS-HARRIS H. Factors associated with reactogenicity following administration of an OMV Meningococcal Vaccine in children aged 8 – 12 years. Public Health Association of Australia 11th National Immunisation Conference Immunisation: old challenges and new frontiers. Surfers Paradise Marriott Gold Coast, 2008.

GRANT CC, GOODYEAR-SMITH FA, TURNER NM, **PETOUSIS-HARRIS HA**. Characteristics of general practices associated with higher immunisation coverage. WONCA European Conference, Paris, France, 17 Oct 2007 - 21 Oct 2007. 2007

GRANT, C.C., **PETOUSIS-HARRIS, H**., TURNER, N., GOODYEAR-SMITH, F., KERSE, N., JONES, R. et al.). General Practice and Health Professional Determinants of Immunisation Coverage: Having a good boat and sailing it well. Keynote presentation. New Zealand Immunisation Conference. TePapa, Wellington. 2007

PETOUSIS-HARRIS, H., GRANT, C., GOODYEAR-SMITH, F., YORK, D., TURNER, N., KERSE, N. et al. The caregiver, the practice and getting immunised - on time: Results for the caregiver component of the Primary Care Determinants Study. New Zealand Immunisation Conference.

TePapa, Wellington. 2007.

YORK, D., GRANT, C., TURNER, N., GOODYEAR-SMITH, F., **PETOUSIS-HARRIS**, H., KERSE, N. et al.. Characteristics of General Practices Associated with Higher Immunisation Coverage. New Zealand Immunisation Conference. TePapa, Wellington 2007

GOODYEAR-SMITH, F., GRANT, C., TURNER, N., **PETOUSIS-HARRIS, H**., YORK, D., KERSE, N. et al.. Characteristics of general practitioners associated with higher immunisation coverage. New Zealand Immunisation Conference. TePapa, Wellington. 2007

DESMOND, N., GRANT, C., TURNER, N., GOODYEAR-SMITH, F., **PETOUSIS-HARRIS**, H., YORK, D. et al. (2007). Practice Nurse Characteristics Associated with Higher Immunisation Coverage. New Zealand Immunisation Conference. TePapa, Wellington

Patents

Other forms of dissemination (reports for clients, technical reports, popular press, etc)

Regular (Quarterly) contribution

Paediatric Vaccines Research Review. Quarterly review of recent research in paediatric vaccines to NZ Health Professionals. Provision of independent commentary each quarter on five recent studies.

New Zealand Doctor

Regular provision of articles

Appendices

Appendix 1: Study Two Eligibility Criteria

PIPS (Pertussis in Pregnancy Safety) Study

Eligibility form for pregnant woman receiving TdaP vaccine at your practice

Inclusion criteria		
1. Is the patient a pregnant woman who has just received the Tdap vaccine during pregnancy between 28 and 38 weeks of gestation?	◯ **Yes**	◯ No
2. Is the patient compliant with routine antenatal care, including at least one ultrasound early in pregnancy?	◯ **Yes**	◯ No
3. Does your practice have the associated information on the specific vaccines given, including batch number?	◯ **Yes**	◯ No

If the answers to **all** the inclusion criteria are '**yes**', please give the potential participant a Patient Participant Information Sheet Summary to read and follow up with the Referral Form.

If the patient is happy to have their contact details passed on to the study team, please make sure they are given a copy of the full Patient Participant Information Sheet and the measuring strip before they leave the practice.

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANT ETHICS COMMITTEE ON **/**/** for *** years. Ref No ****/***

Appendix 2: Study Two Patient Participant Information Sheet

(summary)

Dr Helen Petousis-Harris
Department of General Practice & Primary Health
SCHOOL OF POPULATION HEALTH
The University of Auckland
Private Bag 92019
Auckland, 1142
h.petousis-harris@auckland.ac.nz

Patient Participant Information Sheet Summary

Monitoring the safety of whooping cough vaccine given during pregnancy

We invite you to participate in a study to monitor the safety of whooping cough vaccine given during pregnancy. This study is conducted by the Paediatric Department at the University of Otago, Christchurch and the Immunisation Advisory Centre at the University of Auckland, and is funded by GlaxoSmithKline, the vaccine manufacturer.

Principle Investigators

Dr Helen Petousis-Harris
Senior Lecturer
University of Auckland
Director of Immunisation Research and Vaccinology (IMAC)

Dr Tony Walls
Senior Lecturer
University of Otago
Paediatric Infectious Diseases Specialist

Why are we doing this study?

In October 2012, the Ministry of Health extended their vaccination programme to offer the whooping cough vaccine, free-of-charge, to all pregnant women from 28–38 weeks gestation for the duration of the current whooping cough epidemic. The aim of the Ministry of Health intervention is to prevent whooping cough in small babies who are most at risk of severe infection.

Our study aims to add to the existing knowledge about the safety of the vaccination, by evaluating any possible event occurring after you received the vaccination. Such events might include swelling or redness around the site where you had the injection.

If you would like to find out more about the study, with your consent, the practice nurse will forward to us your contact details along with some demographic information such as your age and ethnicity, information about any underlying medical conditions you may have, and information about the vaccine given and any possible immediate reaction you may have had. A member of the study team will contact you shortly after you received the vaccine, to talk to you and answer any questions you have about the study. If you agree to take part, we will ask you some questions about any 'events' (e.g., injection site reaction, fever) that may have occurred. We will call you again 4 weeks after your vaccination. Any information you give us will be confidential.

Each contact will involve a short telephone interview. In appreciation of your time, after the second phone call we will send you a $40 supermarket or petrol voucher.

***If you agree to us calling you, the practice nurse will give you a clear plastic measuring tool to have ready when we call you. If you agree to take part in the study, and if you do experience any swelling or redness in the place you had the injection, you can use the plastic measuring tool to measure the reaction when we call you.**

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Appendix 3: Study Two Referral Form

PIPS (Pertussis in Pregnancy Safety) Study Referral Form

Practice name:	
Form completed by:	
Date form completed:	
Date vaccination given:	
Vaccine product:	
Vaccine batch number:	
Patient's name:	
Patient's NHI number:	
Patient's date of birth:	
Patient's ethnicity:	
Patient's hme phone no:	
cell phone no:	
Estimated due date:	

If the patient **DOES NOT** consent to be contacted, please complete the ***italicised*** information above only, provide a reason for declining (**see bottom of form**) and return this form to the research team.

1.	Arm in which vaccine was given?	◯ Left	◯ Right
2.	Was there any immediate reaction (within 30mins)?	◯ Yes (please describe reaction)	◯ No
3.	Were concomitant vaccines given?	◯ Yes (what other vaccines?)	◯ No
4.	Has the patient had a previous pertussis booster?	◯ Yes (please provide product name and batch if available) Product…….. Batch no……	◯ No
5.	Does the patient have a history of fever or vaccination reaction?	◯ Yes (please provide details)	◯ No
6.	Does the patient have any underlying health or medical conditions?	◯ Yes (please list conditions)	◯ No

If the patient chooses **NOT** to be contacted about this study, please ask why and select the option below that best

describes their answer:			
◯	Too busy	◯	Unable to be contacted
◯	Dislike being involved in research	◯	Little or no English
◯	Other (please state):		

Thank you for your time. If you have any questions about this form, please feel welcome to call the Principal Investigator Dr Helen Petousis-Harris on (09) 923 6191 or the Project Manager Donna Watson (09) 923 2076.

Fax: Attention Donna Watson IMAC Research (09) 373 7030
Scan and email: d.watson@auckland.ac.nz

Appendix 4: Study Two Consent Form

Dr Helen Petousis-Harris
Department of General Practice & Primary Health
SCHOOL OF POPULATION HEALTH
The University of Auckland
Private Bag 92019 Auckland, 1142
h.petousis-harris@auckland.ac.nz

Patient Consent Form

Monitoring the safety of whooping cough (pertussis) vaccine given during pregnancy

	Tick for yes
• I have read and understood the Patient Participant ion Information Sheet dated **** about the study designed to monitor the safety of whooping cough vaccine administered during pregnancy. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.	☐
• I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.	☐
• I understand that:	
○ taking part in this study is entirely voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my health care. I can also withdraw my information if I choose, up to 10 working days after each of the phone interviews;	☐
○ that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study;	☐
○ anonymised data collected during the study will be made available to the Marketing Authorisation Holder (the product manufacturer) as part of global drug safety surveillance;	☐
○ consent forms will be stored in a locked cabinet on University premises for 10 years then shredded, and information stored electronically will be stored in a password-protected file for the same time period and then irreversibly erased.	☐
• I have had time to consider whether to take part in the study.	☐
• I know who to contact if I have any questions about the study in general.	☐
• I have consented to being contacted by the study team via telephone to discuss any events (e.g., pain, fever, redness or swelling) that occurred around the time of vaccination (approx. 10–15 min phone call).	☐

- I consent to being contacted by a member of the study team one month after my vaccination to complete a phone survey about any events occurring since receiving the vaccine (approx. 5–10 min phone call). ☐
- I understand that after my last phone survey I will be mailed a $40 retail voucher as reimbursement for my time. ☐
- Please indicate which retail voucher you would prefer to receive (circle one):
  - Supermarket
  - Petrol
- I consent to the study team accessing information from the national databases in order to determine outcomes for my baby, such as any notifications of whooping cough. ☐
- Should I experience any reactions or events following immunisation, I consent to my information being shared with the New Zealand Centre for Adverse Reaction Monitoring (CARM). ☐
- I would like to have a summary of the research findings sent to me when the study is over. (Please note that a summary of the findings will be available in approximately December 2014.) ☐

Participant's details:

I _____ (print full name)

of _____ (print address)

_____

_____ hereby consent to take part in this study.

○ Verbal consent of participant received (tick) Date: ___ ___ / ___ ___ / ___ ___ ___ ___
day month year

Email address for scan and email copy of consent form:

_____

(If participant does not have an email address, the copy of the consent form can be mailed.)

Researcher's details:

Full names of researcher: _____

Contact phone number: _____

Project explained by: _____

Signature: _____ Date: ___ ___ / ___ ___ / ___ ___ ___ ___
day month year

Ethical approval

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANT ETHICS COMMITTEE ON **/**/** for *** years. Ref No ****/***

Appendix 5: Study Two Patient Participant Information Sheet (full)

Dr Helen Petousis-Harris
Department of General Practice & Primary Health
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The University of Auckland
Private Bag 92019
Auckland, 1142
h.petousis-harris@auckland.ac.nz

Patient Participant Information Sheet

Monitoring the safety of whooping cough vaccine given during pregnancy

We invite you to participate in a study to monitor the safety of the whooping cough vaccine (Tdap—which contains **t**etanus, **d**iphtheria and **a**cellular **p**ertussis components) given during pregnancy. This study is conducted by the Paediatric Department at the University of Otago, Christchurch and the Immunisation Advisory Centre at the University of Auckland, and is funded by GlaxoSmithKline, the vaccine manufacturer.

Principle Investigators

Dr Helen Petousis-Harris
Senior Lecturer
University of Auckland
Director of Immunisation Research and Vaccinology Immunisation Advisory Centre

Dr Tony Walls
Senior Lecturer
University of Otago
Paediatric Infectious Diseases Specialist

Why are we doing this study?

The purpose of this study is to actively evaluate the safety of the Tdap vaccination in pregnancy, to add greater detail to the existing knowledge base about Tdap vaccination.

Whooping cough can cause severe disease in infants. Most of the infants hospitalised with whooping cough in the last 5 months have been younger than 8 weeks of age and have therefore not had their first whooping cough immunisation. If mothers are vaccinated during pregnancy with a Tdap vaccine this may provide some protection for infants in the first few months of life.

To date, the safety of Tdap immunisation during pregnancy has not been systematically studied. In the USA the Advisory Committee on Immunisation Practices has reviewed the available information on Tdap and concluded that *"…these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine."*

The New Zealand Ministry of Health Technical Advisory Forum on vaccines also reviewed the available safety and effectiveness information for Tdap and recommended the use of Tdap during pregnancy in New Zealand. In October 2012, the Ministry of Health extended their vaccination programme to fund the administration of Tdap to all pregnant women from 28–38 weeks gestation, for the duration of the current whooping cough epidemic. The aim of this intervention is to prevent whooping cough in small babies who are most at risk of severe infection.

What is involved?

If you agree to participate there will be two points of contact with the research team:

1) An initial phone call soon after you receive the vaccine, to explain the study and seek your consent to take part. We will scan and email or post (if email is not available) you a copy of your verbal consent form (signed on your behalf by the researcher) for your records. If you agree to take part in the study we will ask that you use the clear plastic measuring tool provided by your doctor's nurse to measure any immediate reactions such as redness or swelling at the injection site that may have occurred. This call will take approximately 10–15 minutes.
2) A second phone survey 4 weeks after you had the vaccine to ask again about any events that may be associated with the vaccine. This call will take about 5–10 minutes.

To thank you for your time and effort, we will send you a $40 supermarket or petrol voucher following the second phone call.

With your permission, we will determine the outcomes for your baby including any notifications of whooping cough by accessing the national databases. We will not need to contact you or your doctor for this information.

Do you have to stay in the study?

Your participation in this study is entirely voluntary and you may leave the study at any time without giving a reason. If you do give a reason, then it may be recorded. Your choice will not change the medical care or other benefits you receive outside of this study.

You also have the right to withdraw your information up to 10 working days after each of the phone interviews.

What are the risks and benefits of this study?

Your participation will add to the existing knowledge about the safety of Tdap vaccination in pregnancy, and may indirectly benefit unborn children whose mothers may get vaccinated in the future.

This study is only asking pregnant women who have had Tdap vaccine, to take part and to answer questions about receiving the vaccination. There is no risk involved in taking part in the study.

Tdap vaccinations help protect children and adults from diphtheria, tetanus and pertussis infection, but it may have unwanted side effects, such as injection site reactions (e.g., swelling, redness), in some patients. If you have any questions about this, ask your doctor, nurse or pharmacist.

Confidentiality and privacy

It is very important that your personal and medical information is kept confidential and secure.

The information on you and your baby collected during the study will be labelled with a code number. The research team will be the only people who have access to this information. The study data base will not include any information that would allow people not involved in the study to identify you (e.g., your name, address or date of birth). All identifying information will be removed at the end of the study. Anonymised data will be made available to the vaccine manufacturer, GlaxoSmithKline as part of global drug safety surveillance.

Any adverse event that occurs during this study, regardless of the cause, will be reported to the New Zealand Centre for Adverse Reaction Monitoring (CARM) at the University of Otago as per national protocols and to the vaccine manufacturer. No information identifying you or

your baby will be provided to the Marketing Authorisation Holder. This is good practice and not influenced by study participation.

After the study we will send you a summary report of the findings if you say (on the Consent Form) that you would like a copy of this report. Note that this report will be available in approximately December 2014.

Data storage and retention

The consent forms will be stored in a locked cabinet on The University of Auckland premises for a period of ten years and then shredded. Information stored electronically will be kept in a password-protected file for the same period, then irreversibly erased.

Who should you contact if you have questions?

If you have any questions about the study, please contact the Project Manager, Donna Watson (d.watson@auckland.ac.nz or (09) 373 7599 extn. 82076) or the Principal Investigator, Dr Helen Petousis-Harris (h.petousis-harris@auckland.ac.nz or (09) 373 7599 extn. 82078).

For any concerns, you may contact Assoc Prof Raina Elley, Acting Head of Department, (09) 373 7599 extn. 86523. For ethical issues, contact the Chair, The University of Auckland Human Participants Ethics Committee, The University of Auckland, Office of the Vice Chancellor, Private Bag 92019, Auckland 1142. Ph: 09 373 7599 extn. 83711.

Thank you very much for your time and help in making this study possible.

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANT ETHICS COMMITTEE ON **/**/** for *** years. Ref No ****/***

Appendix 6: Study Two Phone Survey 1 (48hrs–7days post vaccine)

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h.petousis-harris@auckland.ac.nz

PIPS Study Patient Participant Phone Interview 1 (48 hours–7days post vaccine)

The following questions ask about your memory of events for the period immediately (within 48 hours) following when you received the dose of Tdap vaccine (whooping cough vaccine).

Since having the vaccine, have you experienced any of the following at the place on your arm where you had the injection?

[Tease out potential symptoms and events related to vaccination eg, distinguish between what may be related to pre/post-pregnancy, "is this more than usual?"]

If you have had any redness or swelling, use the clear plastic measure the practice nurse gave you.

Use the smallest circle you can use to cover all of the redness or swelling, and this will give you the measurement of the reaction. If the reaction is bigger than the biggest circle, use the ruler down the side.

Event	Description/Question	Grade/Response
1a. Redness	Has there been any redness where the injection was given?	
	No redness — go to next question	0
	Yes, take measurement (measure tool used ☐ OR estimate ☐)	1
	>0.0 – <1.0cm	2
	=>1.0 – <2.5cm	3
	=>2.5 – <5.0cm	4
	=>5.0 – <10.0cm	5
	=>10.0 – <15.0cm	6
	=>15.0 – <20.0cm	7
	=>20.0 – <30.0cm	8
	=>30.0cm	9
1b. Induration	Is/was there a hard, woody lump with defined edges, where the injection was given?	
	No induration — go to next question	0
	Yes, take measurement (measure tool used ☐ OR estimate ☐)	1

	>0.0 – <1.0cm	2
	=>1.0 – <2.5cm	3
	=>2.5 – <5.0cm	4
	=>5.0 – <10.0cm	5
	=>10.0 – <15.0cm	6
	=>15.0 – <20.0cm	7
	=>20.0 – <30.0cm	8
	=>30.0cm	9
1c. Swelling	Is/was there any swelling either outside the hard woody lump or without any hard lump in the middle?	
	No swelling — go to next question	0
	Yes, take measurement (measure tool used ☐ OR estimate ☐)	1
	>0.0 – <1.0cm	2
	=>1.0 – <2.5cm	3
	=>2.5 – <5.0cm	4
	=>5.0 – <10.0cm	5
	=>10.0 – <15.0cm	6
	=>15.0 – <20.0cm	7
	=>20.0 – <30.0cm	8
	=>30.0cm	9
1d. Pain intensity	Is/was there any pain where the injection was given?	
	No pain — go to next question	0
	Yes, to what extent	1
	• Mild, still able to move arm normally	2
	• Moderate, hurts to move arm normally or to touch	3
	• Severe, unable to move arm	4

1e. Interval and **duration** for onset of local event or first observation

Where applicable, how long after having the vaccination did the event occur? Circle as appropriate. **How long did the event last?**

Redness	**Duration**	Induration	**Duration**	Swelling	**Duration**	Pain	**Duration**
>0 – 24hrs	>0 – 24hrs	>0 – 24hrs	>0 – 24hrs	>0 – 24hrs	>0 – 24hrs	>0 – 24hrs	>0 – 24hrs
24 – 48hrs	24 – 48hrs	24 – 48hrs	24 – 48hrs	24 – 48hrs	24 – 48hrs	24 – 48hrs	24 – 48hrs
49 – 72hrs	49 – 72hrs	49 – 72hrs	49 – 72hrs	49 – 72hrs	49 – 72hrs	49 – 72hrs	49 – 72hrs
73hrs – 7 days	73hrs – 7 days	73hrs – 7 days	73hrs – 7 days	73hrs – 7 days	73hrs – 7 days	73hrs – 7 days	73hrs – 7 days
>7 days		>7 days		>7 days		>7 days	

1. Did you feel feverish after you received the vaccine?		
	No fever — go to question 2c	0
	Yes, had fever	1
2a.	How long after the vaccine did the fever occur?	
	0–4 hrs	1
	5–8 hrs	2
	9–24 hrs	3
	or after 24 hrs?	4
2b.	Was the temperature measured?	
	Temperature not taken	0
	Temperature taken but don't know what it was	1
	Temperature taken and read as below:	
	<38°C	2
	38.0–38.4°C	3
	38.5–38.9°C	4
	39.0–39.4°C	5
	39.5–39.9°C	6
	40.0–40.4°C	7
	40.5–41.0°C	8
2c.	Was anti-fever/pain medicine given or did you take anti-fever/pain medicine? (e.g., panadol/nurofen)	
	No meds given/taken — go to question 3	0
	Yes, meds given/taken	1
	Don't recall	88
2d.	Was it given/taken before or after vaccination?	
	Before	1
	After	2
	Both	3
	Don't recall	88
2. Did you have any other symptoms after you received the vaccine?		

	No — go to question 4	0
	Yes — circle below as appropriate	1
	Events	
	Nausea, vomiting or diarrhoea	1
	Headache	2
	Fatigue, lethargy or general weakness	3
	Events around the area where you got the injection (other than those already discussed)	4
	Pain (including muscle or joint pain: not injection site pain)	5
	Intense shivering/Shaking	6
	Other (details)	7
3. Did you need to see or call the doctor for any reason in the 24–48 hours after having the vaccine?		
No, did not need to contact the doctor — go to question 5		0
Yes, did need to contact the doctor		1
Who did you see?		
Where?		
For what reason?		
Can we contact your doctor for more information?		Yes / No
4. Other than the vaccine you just had, have you received the Tdap (Boostrix®) vaccine (whooping cough) previously?		
No, not had Tdap before — go to end		0
Yes, had Tdap before (may need prompt, eg, if they have had tetanus in recent years)		1
Don't know — go to end		88
Can you remember which brand it was? What brand was it?		Yes / No

Ethical approval

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANT ETHICS COMMITTEE ON **/**/** for *** years. Ref No ****/***.

Appendix 7: Study Two Phone Survey 2 (4-weeks post vaccine)

PIPS Patient Participant Phone Survey (4 weeks post vaccine)

Researcher: _____ Date: _____

The following questions ask about your memory of events for the period up to 4 weeks following when you received the Tdap vaccine (whooping cough vaccine).

	Yes	No	Date started	Date resolved/ recovered	Resolving/ recovering	Not resolved/ recovered	Resolved/ recovered with lasting effects
1. Have you experienced any adverse events/symptoms within the one month post vaccination?							
2. Since receiving the vaccine, have you had any infections such as: urine; ear; nose; throat; lung infections; gastroenteritis; skin infections							
3. Since receiving the vaccine, have you experienced any of the following:							
Muscle aches and pains							
New onset high blood pressure							
Severe nausea or vomiting							

Premature labour							
Premature rupture of membranes							
Severe abdominal pain							
Vaginal bleeding							
Depression or psychological disorders							
Unexplained itching of the skin							
Spontaneous abortion or threatened abortion							
4. Since receiving the vaccine, have you needed to see a doctor for any of the events described above or for any other reason?		If no, go to end.	If yes, please indicate where you saw the doctor: ○ Emergency Room/After Hours ○ Hospital ○ GP Practice				
4b. What was the diagnosis?							
4c. If there was no diagnosis, what were the signs and symptoms?							

4d. Can we contact your family doctor for further details? (If yes, please provide Dr name and hospital/practice details)

Appendix 8: Canterbury Protocol

PROTOCOL

Observational study: safety of Tdap administered during pregnancy

Investigator-sponsored study with GSK support

Principle investigator:

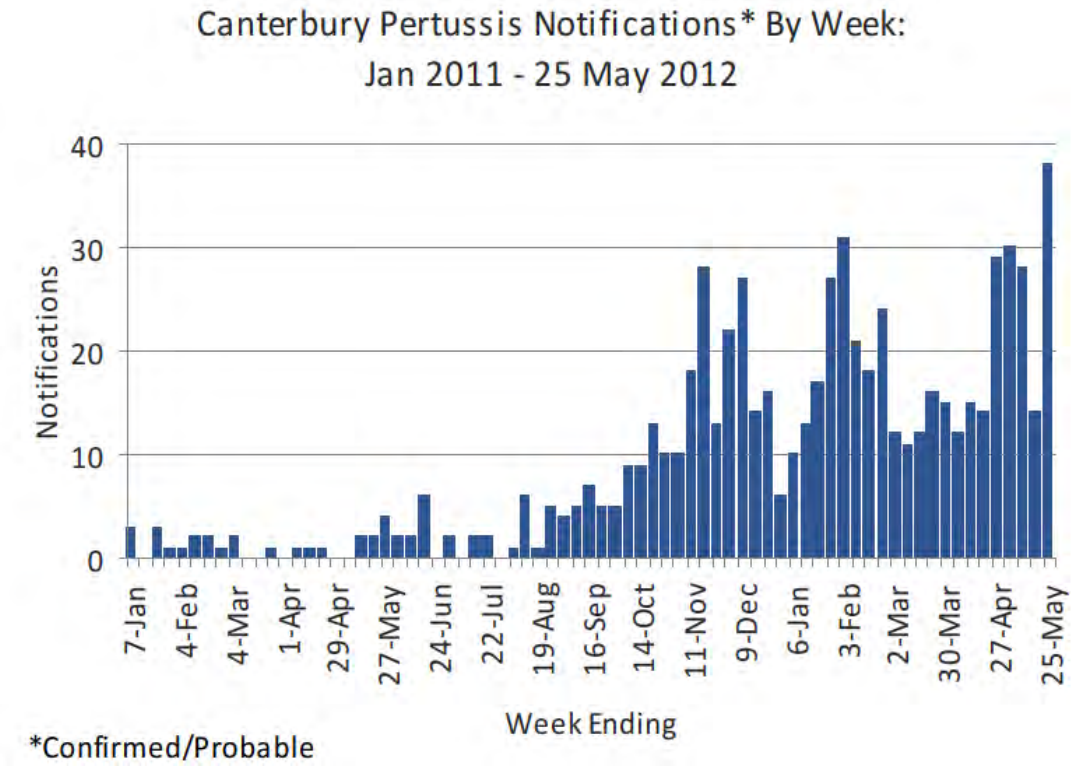
Dr Tony Walls FRACP, MD

Paediatric Infectious Diseases Specialist

Senior Lecturer, Department of Paediatrics

University of Otago, Christchurch

Background: The Canterbury region is currently experiencing an outbreak of pertussis (whooping cough) with rates of laboratory confirmed disease 10x greater than baseline.[11] Most of the infants hospitalised with pertussis infection in the last 5 months have been younger than 6 weeks of age and have therefore not received their first pertussis immunisation.11 Data in New Zealand shows about 20% of infant cases are infected by their mothers.[12]



Young infants are generally not protected from pertussis as they are un-immunised and only small amounts of protective antibodies are transferred across the placenta. The main reason

[11] Institute for Environmental Science and Research. ESR Pertussis Report; Weeks 14 - 15: 31 Mar – 13 Apr 2012. Wellington: ESR; 2012. Available at http://www.surv.esr.cri.nz/PDF_surveillance/PertussisRpt/2012/201214PertussisRpt.pdf

[12] Walls R. Pertussis (whooping cough) epidemiology in Waikato, New Zealand: 2000–2009. *NZ Med J* 2011;124(1332).

for minimal protection from maternal antibodies is the waning of maternal immunity and low antibody titres in most pregnant women.

Recently the US Advisory Committee on Immunization Practices (ACIP) recommended that acellular pertussis vaccine (Tdap) be given to any person likely to be in contact with young infants under the age of 12 months, including pregnant women.[13] Administering the vaccine to pregnant women is advised because it not only protects the mother from pertussis but also induces antibodies for the infant at birth which may be protective.3

ACIP acknowledged that the safety of Tdap immunisation during pregnancy has not been systematically studied, with the only data available coming from small studies, postmarketing surveillance, and the the US Vaccine Adverse Event Reporting System (VAERS).[14] They concluded that *"available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine."*4

The NZ Ministry of Health's Immunisation Technical Forum (ITF) on vaccines reviewed this recommendation in 2011 and has now recommended the use of Tdap during pregnancy in New Zealand (after 20 weeks).[15] The Ministry of Health also recommends and funds (i.e the vaccine is given at no cost to the woman) influenza vaccination for all pregnant women in NZ.[16]

With this in mind, a District Health Board in Canterbury (CDHB) has agreed to fund the administration of Tdap during the current pertussis outbreak to pregnant women (30-36 weeks) and to women in the first 2 weeks after birth.[17]

For GPs to be paid for administering the vaccines they need to submit a correctly completed claim form to the CDHB. The usual pratice is to submit the claim immediately after the vaccine is given and we would anticipate finding that a claim had been submitted within 1 week of its submission.

Study objectives

Primary Objectives:

- To describe adverse events in women who were administered Tdap between 30-36 weeks of gestation
- To describe outcomes of babies whose mothers were vaccinated with Tdap during week 30 to 36 of pregnancy (including birth history, weight and head circumference and any congenital abnormalities)

Secondary Objectives:

- To describe adverse events in women who were administered the seasonal influenza vaccine during pregnancy
- To describe adverse events in women who were administered the seasonal influenza vaccine and Tdap during pregnancy

[13] United States Centers for Disease Control and Prevention. Updated recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; 60(41): 2011

[14] US Advisory Committee on Immunization Practices. Summary Report. Atlanta, Georgia: ACIP; February 23-24, 2011. Available from http://www.cdc.gov/vaccines/recs/acip/downloads/min-feb11.pdf Accessed 23 April 2012.

[15] New Zealand Ministry of Health. Current advice on the public health management of pertussis. Wellington: MoH; 5 April 2012. Available at http://www.nzdoctor.co.nz/media/1682109/pertussis_letter_moh_5_apr_2012.pdf

[16] New Zealand Ministry of Health. Chapter 15: Influenza. In Immunisation Handbook 2011. Wellington: MoH; 2011. Available at http://www.google.co.nz/url?sa=t&rct=j&q=ministry%20health%20influenza%20vaccine%20pregnant%20women%20funded%20&source=web&cd=7&ved=0CGYQFjAG&url=http%3A%2F%2Fwww.health.govt.nz%2Fsystem%2Ffiles%2Fdocuments%2Fpublications%2F15influenza.pdf&ei=8SiWT8iDH4_m8QOgnNGMCg&usg=AFQjCNFUuAYDXQKxJFmtqXKd4PBfzm1i2A

[17] Canterbury District Health Board. Media release from Canterbury DHB: Free whooping cough vaccine extended to pregnant women. Christchurch: CDHB; April 19, 2012.

- To compare adverse event rates in women who were vaccinated with Tdap, seasonal influenza vaccine or both
- To describe outcomes of babies whose mothers were vaccinated with the seasonal influenza during pregnancy (including birth history, weight and head circumference and any congenital abnormalities)
- To describe outcomes of babies whose mothers were vaccinated with the seasonal influenza and also received Tdap during weeks 30-36 of pregnancy (including birth history, weight and head circumference and any congenital abnormalities)
- To Evaluate infants of mothers vaccinated with Tdap, seasonal influenza vaccine or both during pregnancy who have symptoms consistent with pertussis or who have had significant contact with a proven case

Study design

This is a prospective observational cohort study. It will describe any adverse events in pregnant mothers who received either Tdap or influenza vaccine, or both. Outcomes for their infants will also be measured and described. Infants of mothers vaccinated with Tdap, seasonal influenza vaccine or both during pregnancy who have symptoms consistent with pertussis or who have had significant contact with a proven case will also be evaluated. The funded branded of Tdap are Boostrix and Adacel, and the funded brands of influenza are Fluarix and Fluvax).

Study population

Women vaccinated during pregnancy with Tdap will be identified through the GP record of claims for the administration of the vaccine as soon as possible after administration of the vaccine. Women from the same GP practices who have had trivalent inactivated influenza vaccine during pregnancy will also be identified and enrolled..

It is possible women may have received Tdap from sources other than their GP e.g. healthcare workers or women who are seen at hospital with wounds that require a tetanus booster. However it is anticipated this will only be a very small proportion, and the records of claims through the CDHB will accurately reflect the total number of women in Canterbury receiving Tdap during pregnancy.

Identification of women receiving vaccination

Women will be identified as having received vaccination through the claims data submitted to the CDHB. The consent for for Tdap vaccine also asks women if they are happy to be contacted by the study team. Contact details will be obtained from their GP only for women who have indicted they are happy to be contacted.

Informed consent

The Claim form contains basic consent for participation in the study, but an additional consent form (Appendix 1) will be used to obtain signed informed consent for participation and handling of personally identifiable information and safety data.

If a woman choses not to participate or to withdraw from the study at a later date the reason for non-participation or withdrawal will be recorded.

Confidentiality

Data will be collected and stored on a password protected database located in the Paediatric Department at Christchurch Hospital. The NHI will be used during data collection to identify study participants alongside a study identification number. The study identification number will not include any details that could potentially identify the study participant i.e. date of

birth. The NHI is included because it will provide the easiest access to information from GP records, particularly for newborn infants who may change surnames.

Prior to any data analysis the NHI will be removed from the database and just a study identification number will be used.

Expected sample size

The birth cohort in Canterbury is approximately 6000 per annum. Seasonal influenza vaccines are available in NZ between March and July. Both Tdap and influenza vaccine are funded for pregnant women, but it is very difficult to estimate how many women will take up the vaccines. As of 31st May 2012, 220 claims for the Tdap vaccine had been lodged with the CDHB in 6 weeks. At the 10th June, out of 255 claims processed 22 women had not consented to follow up. There were also a further 53 claims that have been rejected and returned to practices mainly as the consent yes or no was not completed.

Funding for Tdap is being offered postpartum as well as during pregnancy, so women may choose to wait until their babies are born to take up the offer. Funding for the vaccine has approved for an initial period of 6 months with a view to extending for another 6 months if the pertussis outbreak continues. Previous outbreaks in New Zealand have lasted in the order of 18 months so it is likely that funding will continue beyond 6 months. We would therefore aim to enroll 300 women who have received Tdap vaccine.

Study groups

Group 1) received Tdap vaccine while pregnant (30 to 36 weeks gestation).

Group 2) received trivalent inactivated influenza vaccine while pregnant

Group 3) received both Tdap and trivalent inactivated influenza vaccine, separately or coadministered during pregnancy

Inclusion criteria

Women

- Pregnant women 18-40 years of age who have received either the Tdap vaccine between 30-36 weeks gestation, or received the influenza vaccine at any stage during pregnancy or both
- Compliant with routine antenatal care, including at least 1 ultrasound early in pregnancy
- Information regarding which brand vaccine of was given (if the brand is not available, batch number and expiry is sufficient as this will help to ascertain which brand was given)

Infants:

- Infants of the women who were vaccinated with the Tdap vaccine, seasonal influenza vaccine or both during pregnancy

Exclusion criteria

- Pregnant women who have received the Tdap vaccine prior to 30 weeks gestation or after 36 weeks gestation
- If a woman has already had her baby prior to being contacted by the the study team, she will not be enrolled in the study

Statistical Analysis

As this study is an observational study, the pregnancy outcomes and safety data will be descriptive in nature. The rates of AEs and SAEs will be compared to published background rates for the general population (summarised in Tavares et al[10]). The expected rates of MAEs and SAEs for Tdap given during pregnancy is unknown, but as a guide the rates of MAEs for pregnant women receiving influenza vaccine in this paper ranged from 1.1 to 3.8% while the rate of SAEs ranged from 0.4 to 1.5%. Where the known background incidence of 0.01 for a particular adverse event, a sample size of 300 achieves 80% power to detect an additional incidence rate of 0.0175 when the significance level is 0.05.

It is anticipated that the difference in AEs between subgroups in the trial will be small. As this is an observational study we therefor plan to describe the confidence intervals for the proportions of AEs within each group. A sample size of 300 produces a two-sided 95% confidence interval with a width equal to 0.081 when the sample proportion is 0.150.

Women who have multiple pregnancies and/or complicated pregnancies will be excluded from the final analyses and described separately.

Related research

In studies of pertussis booster vaccines administered alone or together with influenza vaccine in people 19–64 years of age,[18] adverse reactions were generally mild-to-moderate in intensity. The overall reactogenicity profile of the Tdap and influenza vaccines, in terms of incidence of solicited local symptoms (injection site pain, redness and swelling), as well as the incidence of solicited general symptoms (fatigue, fever, gastrointestinal symptoms, headache, joint pain, muscle aches, and shivering) was generally similar between the co-administration and sequential vaccine groups (Figure).[8] The most frequently reported local and general solicited symptoms in both vaccine groups were injection site pain and muscle aches, respectively.[8] Unsolicited adverse events were reported by similar percentages of subjects in both groups (about 20%).[8]

The local symptom report rate was 48.9% after *Fluarix* and 61.6% after *Boostrix*. The rate of unsolicited AE reporting was 17.4% (14.7-20.3) after *Fluarix*, 14.6% (12.1 to 17.3) after *Boostrix*, and 21.5% (18.6-24.6%) after co-administration with both vaccines. The report rate of unsolicited AE causally related to vaccination was 4.3% (2.9 to 6.0) after *Fluarix,* 2.4% after *Boostrix* (1.4-3.8) and 7.0% (5.2-9.0) after co-administration.

The *Boostrix* Data Sheet notes that when Tdap and seasonal influenza vaccine are coadministered in adults, lower levels of antibodies to FHA and pertactin are induced compared to Tdap alone.[19] It is not known if the efficacy of *Boostrix* is affected.[9]

[18] Weston WM et al. Safety and immunogenicity of a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine when co-administered with influenza vaccine in adults. *Hum Vaccin*. 2009;5(12):858-66.
[19] GlaxoSmithKline New Zealand. *Boostrix* Data Sheet. GSKNZ; 2011. Available at www.medsafe.govt.nz
[10]Tavares et al Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: A prospective cohort study. Vaccine 2011;29:6358

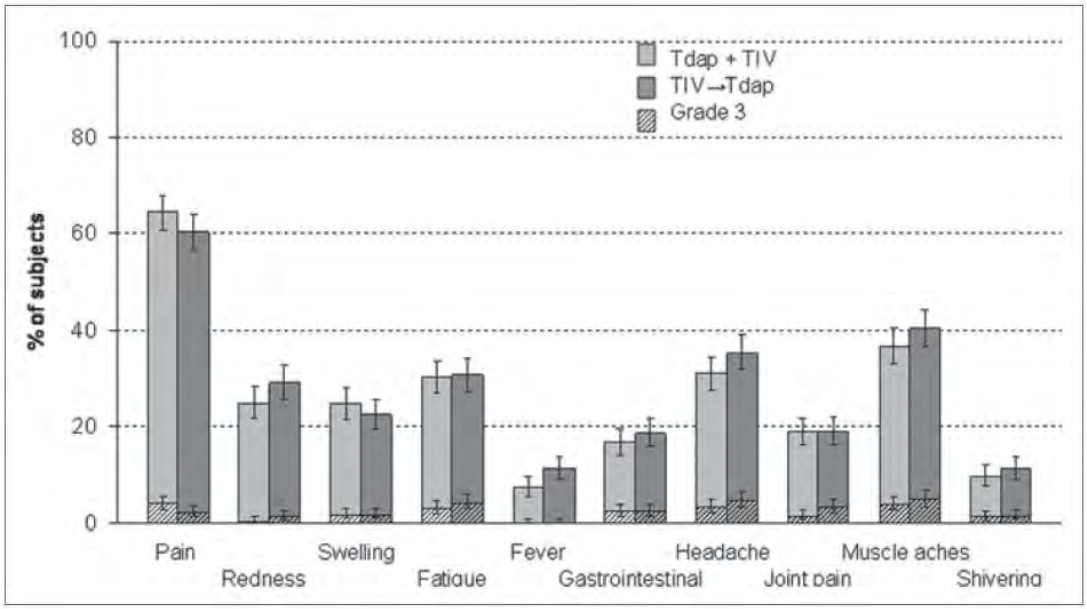


Figure: Percentage of subjects 19–64 years with solicited local and general symptoms during 15 days after vaccination

Fever = oral temperature ≥37.5°C (99.5°F). Grade 3 referred to redness and swelling of diameter ≥50 mm; oral temperature >39.0°C (>102.2°F); and for all other symptoms, prevented normal activity. From Weston et al, 2009.[8]

Study assessments and procedures

Scheduled assessments	Adverse events in mother	Outcomes for infant	Both mother and baby
At enrolment	[1]**First contact with mother by phone** (standard script, *Appendix 2*) as soon as possible after identification to • Provide information about study and obtain detailed informed consent for participation (written consent form sent out if verbal consent given by phone) • capture any solicited adverse events within first 48 hours and first 7 days of receiving vaccine (s) Contact GP once consent obtained to obtain details of vaccination *(Appendix 3)*		Contact with mother monthly either by phone or e-mail[4]. If infant has symptoms* consistent with pertussis or a significant contact** with proven case will be invited for clinical review by study team Paediatrician. If an unsolicited adverse event is noted during these calls, it will follow the same safety reporting procedures as other AEs in the study.
4 weeks since vaccine administration	[2]**Written questionnaire** *(Appendix 5)* to capture any solicited adverse events in mother up to 4 weeks after receipt of vaccine (s)		
6-week check	**Written questionnaire** (*Appendix 6*) administered by telephone to GP to	**Written questionnaire** (*Appendix 6*) administered by telephone to GP practice to	

	determine pregnancy outcome and medically attended adverse events in mother since last contact.	capture birth history, weight and head circumference, any congenital abnormalities, neonatal death (<29 days) Details of 6-week check and confirm receipt of 6-week vaccination. Document any prior GP or hospital visits.	
3-6 month check		Weight, head circumference, vaccination status, and standardised clinical examination by Plunket Nurse as recorded in Well Child book *(Appendix 6)*.[3]	
1-year follow-up		Final contact with mother about pertussis exposure and/or symptoms. Vaccination status – if not completed infant vaccinations by 6 months.	

[1] Three attempts will be made to contact mother by telephone within 1 week of notification of receipt of Tdap. If an e-mail address is available this will also be used if telephone contact is unsuccessful.

[2] Written questionnaire will be sent to mother before 4 weeks have elapsed since receipt of vaccine. Telephone contact will be made at 4 weeks of receipt of vaccine and two further times if the completed questionnaire has not been received within 1 week.

[3] mothers will be encouraged to attend Plunket for checkups during the first 6 months. If there is no available recorded weight and head circumference between 3-6 months of age this will be done by a member of the the study team. The mother will be contacted 3 times via email or phone to get this information.

[4] Three attempts will be made by phone or email to contact the mother each month

*Persistant cough lasting for >10 days and/or post-tussive vomiting

** Close contact defined as being in the same room as the person for > 1 hour or 5 minutes of face to face contact with a person with proven pertussis who was symptomatic.

Study instruments

Appendix 1: Consent form

Appendix 2: Information sheet for mother

Appendix 3: Structured questionnaire for GP practice – information on mother

Appendix 4: Telephone survey questionnaire (adverse events in mother)

Appendix 5: Written questionnaire (medically attended adverse events in mother in first 4 weeks after vaccine)

Appendix 6: Structured questionnaire for GP practice (Details of pregnancy outcomes, standardised clinical examination of baby at 6-week check)

Appendix 7: Information from clinical examination by Plunket Nurse between 3-6 months of age (outcomes for infant)

Appendix 8: Monthly surveillance questions for mother and infant

Reporting

It will still be the responsibility of the physician administering the vaccine to report any adverse events using the local reporting system.

The study team will also report any adverse events to:

o Local pharmacovigilance agency (CARM – Centre for Adverse Events Monitoring, University of Otago, website: carm.otago.ac.nz)

Adverse Event and Serious Adverse Event Definitions

An Adverse Event (AE) shall mean any untoward medical occurrence whether thought to have been caused by the vaccines or not and Serious Adverse Event (SAE) shall mean any adverse event which is fatal, life threatening, disabling or incapacitating, requires in-patient treatment or prolongs existing hospitalization, is a congenital anomaly in the off-spring of the patient or which may require intervention to prevent the previously stated outcomes.

If there is a report of an unsolicited event during phone calls with the mother regarding pertussis symptoms in the baby- this will follow the same reporting as above.

Budget

	NZD
Research Nurse 0.5 FTE for 1 year	35,000
Research Nurse 0.5 FTE for 1 year	35,000
Database and statistical support	15,000
Publication and Reporting	3000
Consumables	1500
Total	89,500

Study Milestones:

July 2012	First participants enrolled in study	
December 2012	Last participants enrolled in study (this potentially may be extended depending on enrollment	
July 2013	Interim report due	
December 2013	Last of the 1 year follow up data will be collected	
March 2014	Final study report due	
May 2014	Submission of publication	

Ethics Approval

The GP claim forms for administration of Tdap includes a section for the woman to indicate if she is willing or not to be contacted by researchers.

This study has been approved by Upper South A Regional Ethics Committee – approval **URA/12/EXP/021**.

Appendix 1: Consent form

Canterbury District Health Board
Te Poari Hauora ō Waitaha

University of Otago
Te Whare Wānanga o Otāgo
New Zealand

Consent form

Study Title: Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy

Investigators:

- Dr Tony Walls, Paediatric Infectious Diseases Specialist, Senior Lecturer, University of Otago, Christchurch.

- Assoc. Professor Nicola Austin, Director Neonatal Service, Christchurch Women's Hospital.

- Assoc. Professor Dee Mangin, Director Primary Care Research Unit, Christchurch School of Medicine.

Venue: Research Office, Neonatal Service, Christchurch Women's Hospital, Christchurch

I have consented to being contacted by the study team via telephone to discuss any adverse events (e.g. pain, fever, redness or swelling) that occurred around the time of vaccination.	Yes	No
I consent to being contacted by a member of the study team one month after my vaccination to complete a written questionnaire about possible adverse events related to the vaccine	Yes	No
I consent to the researchers contacting my General Practitioner's team to obtain information about my pregnancy, the birth of my child, and my child's growth, development and vaccination status during the first 12 months of life	Yes	No
I consent for the researchers to contact me via phone call or e-mail monthly during my child's first year of life to answer some simple questions about symptoms of pertussis	Yes	No

I have read and I understand the information sheet for volunteers taking part in the study designed to monitor the safety of pertussis vaccine administered during

pregnancy. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had the opportunity to use family/whānau support or a friend to help me ask questions and understand the study.

I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my health care.

I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.

I have had time to consider whether to take part in the study.

I know who to contact if I have any questions about the study in general.

I, _____ have read the information sheet about this study and agree to participate.

Signed _____Date _____

Appendix 2: Information sheet for mother

Canterbury District Health Board
Te Poari Hauora ō Waitaha

University of Otago
Te Whare Wānanga o Otāgo
New Zealand

Study Title: Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy

Investigators:

- Dr Tony Walls, Paediatric Infectious Diseases Specialist, Senior Lecturer, University of Otago, Christchurch.

- Assoc. Professor Nicola Austin, Director Neonatal Service, Christchurch Women's Hospital.

- Assoc. Professor Dee Mangin, Director Primary Care Research Unit, Christchurch School of Medicine.

Venue: Research Office, Neonatal Service, Christchurch Women's Hospital, Christchurch

What are the aims of this study?

The Canterbury region is currently experiencing an outbreak of pertussis (whooping cough) with rates of disease 10 x greater than normal. Pertussis can cause severe disease in infants, and most of the children hospitalised with pertussis in the last 12 months have been younger than 8 weeks of age. Most of these infants have not received their first infant immunisations, and therefore have no protection against pertussis. If their mothers are vaccinated during pregnancy with Tdap vaccine (contains tetanus, diptheria and acellular pertussis components) this may provide some protection for them in the first few months of life.

To date, the safety of Tdap immunisation during pregnancy has not been systematically studied. In the USA the advisory committee on immunisation practice (ACIP) has reviewed the available information on Tdap and concluded that *"…these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine."*

The New Zealand Ministry of Health Technical Advisory Forum on vaccines has also reviewed the available information on the safety and effectiveness of Tdap and recommended the use of Tdap during pregnancy in New Zealand.

With this in mind the Canterbury District Health Board (CDHB) has agreed to fund the administration of Tdap during the current pertussis outbreak to pregnant women who have not received a previous pertussis booster with Tdap. The aim of this intervention is to prevent pertussis in small babies who are most at risk of severe infection.

The purpose of this study is to actively evaluate the safety of this new intervention and compare the rates of adverse events following vaccination to those that may occur following influenza vaccination during pregnancy.

What does this study involve?

We are collecting information on any possible adverse events that may occur following vaccination with either Tdap or influenza vaccination. We will also collect information on your baby's health during the first year of life to see if they have been exposed to or had symptoms of pertussis.

If you receive Tdap vaccine, influenza vaccine, or both during pregnancy this information will be routinely passed on by your GP to the CDHB when they make a claim for funding. A member of the research team will then contact you to ask if you would like to participate in the study.

If you agree to participate there will be 3 separate phases of contact with the research team:

- Initial phone survey to obtain consent and determine any immediate adverse events that may have occurred around the time you received the vaccine. This will involve a short telephone interview and if you agree to take part in the study a written consent form will be sent to you.
- At 4 weeks after you received the vaccine we will send you a short survey form to fill in about any adverse events that may have happened in the first 4 weeks after receiving the vaccine.
- Once your baby is born we will be in touch every month up until your baby turns one to ask about possible exposure to pertussis and any illness in your baby that could be pertussis. If your baby is seen by Plunket (or alternative provider) between 3-6 months of age we will contact you around this time to find out about your baby's growth and development as recorded by your Health Nurse.

In addition we will contact your GP to find out details about the following:

Your baby's birth, birth weight, and head circumference.

The findings on your baby's 6-week check – including their weight and the findings of their clinical examination

Your baby's vaccination status

Please note:

If your baby does develop symptoms of pertussis during the follow-up period we will arrange for them to be reviewed by one of the study team doctors.

Do you have to stay in the study?

You may choose to leave the study at any time, without giving a reason. If you do give a reason, then it may be recorded. Your choice will not change the medical care or other benefits you receive outside of this study.

What about your personal and medical information?

It is very important that your personal and medical information is kept confidential and secure.

The information on you and your baby collected during the study will be labelled with a code number. The research team will be the only people who have access to this information. The study data base will not include any information that would allow people not involved in the study to identify you e.g. your name, address or date of birth.

Who should you contact if you have questions?

If you have any questions please contact a member of the study team.

Trish Graham
Research Nurse
NICU
Christchurch Women's Hospital
Private Bag 4711
Christchurch 8011
03) 3644 741
Trish.graham@cdhb.health.nz

Dr Tony Walls
Senior Lecturer
Paediatric Infectious Diseases Specialist
University of Otago
Christchurch
(03) 3640 640
EXT 86536

Appendix 3: Structured questionnaire for GP practice – information on mother

Study Title: Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy

Participants are identified by their NHI (National Health Index) number to prevent duplications and ensure only one survey per participant is possible. The NHI numbers are removed prior to data analysis.

Data collected at the practice will include:

GP Name of Practice where woman is enrolled PHONE	
Name of woman who received vaccination Address	
Contact phone number of woman Email	
NHI number *(this is not to provide identification but only used to ensure that there are no duplications of surveys)*	
Date of Birth (of the woman)	
Ethnicity i.e. Maori/Pacific Island/NZ European/ Other.....	
Estimated due date *(used to work out gestational age)*	
Date of vaccine administration	

Arm which vaccine(s) were given in	
Vaccine product name and batch number	
Any immediate (within 30 minutes) side effects?	
Any other observations?	
Concomitant vaccines administered	
Previous pertussis booster given	
History of fever or vaccination reaction	
Health and underlying medical condition	
Inclusion Criteria:	
Received Tdap after 30 weeks gestation	Yes/No
Compliant with routine antenatal care, including at least 1 ultrasound early in pregnancy	Yes/No
Exclusion criteria:	
Receipt of Tdap (pertussis) vaccination before 30 weeks	Yes/No

Appendix 4: Telephone survey questionnaire (adverse events in mother)

Study Title: Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy

The woman will be asked to provide data that will include the following for the period immediately following each dose of Tdap or influenza vaccine is received:

- Did she have any symptoms immediately after receiving the vaccination? (Yes/No)
  later same day next day lasted-
- Was there any local reaction in the arm where the vaccination was given? (Yes/No)
  or -see bel for details of classification
- Recall of fever (Yes/No) if yes what time frame did the fever– see below for details of classification
- Was the temperature measured? (Yes/No) if yes what was the measured temperature? – see below for details of classification
- Was there any other reactions
  - Nausea, vomiting or diarrhoea
  - Headache
  - Fatigue, lethargy or general weakness
  - Injection site reactions
  - Pain (including muscle or joint pain: not injection site pain)
  - Rigors/Shaking
  - Other (details)
- Was anti-fever medicine given (Yes/No) if yes was it given before or after vaccination?
- Did you need to call or see a doctor? (Yes/No) if yes who, where and why
- Had she received the Tdap vaccine previously? (Yes/No)if yes can she remember which brand it was?
- Can we contact them for more information (Yes/No)

All as per Brighton Collaboration where these definitions are available.[2 3]

Definitions for local reactions and fever	
Local Reactions	**Systemic Events**

Level one diagnostic certainty is:
Any description of morphological or physiological change at or near the injection site that is described or identified by a health care provider
 	
Level two diagnostic certainty is:
Any description of morphological of physiological change at or near the injection site that is described or identified by another person
	Fever
	Endogenous elevation of at least one measured body temperature of ≥38°C
	• Time intervals
	  ○ 0 – 24hr Day 1
	  ○ 0 – 24hr Day 2
	  ○ Day 3-7...
	• Increments

Categories for event classification • Level 1: as specified in the case definition for a local reaction • Level 2: as specified in the case definition for local reaction Insufficient evidence for a local reaction Not a case of a local reaction *Interval for onset of local reaction or first observation* • >0-24 h • 25-48 h • 49-72h • 73h – 7 days • >7 days • Include numbers of subjects with local reactions newly present at each specified time as %. *Diameter of the local reaction* • >0.0 - <1.0 cm • ≥1.0 – 2.5 cm • ≥2.5 – 5.0 cm • ≥5.0 - <10.0 cm • ≥10.0 - <15.0 cm • ≥15.0 - <20.0cm • ≥20.0 - <30.0 cm • ≥30.0 cm Pain scale to include measure of functionality • 0 = No pain • 1 = Mild, still able to move arm normally • 2 = Moderate, hurts to move arm normally or to touch • 3 = Severe, unable to move arm	○ <38°C ○ 38.0-38.4°C ○ 38.5-38.9°C ○ Etc.... >41°C

Appendix 5: Written questionnaire (medically attended adverse events in mother in first 4 weeks after vaccine)

Period_____ to _____

	Yes	**No**	**Date started**	**Date Resolved**	**Resolving**	**Not Resolved**	**Resolved with lasting effects**
Have you experienced any adverse events within the one month post vaccination?							
Any infections							
For example**:* *urine infections, ear, nose, throat or lung infections, gastroenteritis, and skin infections.* ***Circle which one.							
Muscle aches and pains							
New onset high blood pressure							
Severe nausea or vomiting							
Premature labour							
Premature rupture of membranes							
Severe abdominal pain							

Vaginal bleeding							
Depression or psychological disorders							
Unexplained itching of the skin							
Spontaneous abortion or threatened abortion							
2. Have you needed to see a doctor for the adverse event described above or for any other reason in the last month post-vaccination?							
☐ Emergency Room/After Hours ☐ Hospitalisation ☐ GP Practice							
2b. What was the diagnosis?							
2c. If there was no diagnosis, what were the signs and symptoms?							

2a. Can we contact the doctor for further details? (If yes- provide Dr name and hospital/practice details)

Appendix 6.1 and 6.2: Structured questionnaire for GP practice (Details of pregnancy outcomes, standardised clinical examination of baby at 6-week check)

Study Title: Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy

Pregnancy outcomes:	
Date of delivery	
Mode of delivery i.e. Vaginal Elective section Emergency section Forcepts, or ventouse	
Name	
gender	
Complications related to birth Ie admitted to nicu (Provide details)	
Information about infant:	NHI – Apgars 1….. 5 …..10…..
Birth weight (gms)	
Length (cm)	
Head circumference (cm)	
Presence of congenital abnormalities	Yes/No

	If Yes, details.....
Gestational age at birth	Weeks_____

Study Title: Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy

6 week check with GP	
Medically attended adverse events since birth	Yes ☐ No ☐ Hospitalisation ☐ Emergency ☐ GP Practice ☐ Diagnosis: .....
weight	
Length (cm)	
Head circumference (cm)	
Presence of congenital abnormalities	Yes ☐ No ☐ If Yes, details.....
Details of 6-week check	Eye abnormalities Yes ☐ No ☐ Heart abnormalities Yes ☐ No ☐ Lung abnormalities Yes ☐ No ☐ Neurological abnormalities Yes ☐ No ☐ Hip or musculoskeletal abnormalities Yes ☐ No ☐
Receipt of 6-week vaccination	Yes ☐ No ☐

	Date:.....
Receipt of 3 month vaccination	Yes ☐ No ☐ Date:.....

Appendix 7: Information from clinical examination by Plunket Nurse between 3-6 months of age (outcomes for infant)

Study Title: Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy

Information to be collected from Well Child book from any assessment from a Carer between the ages of **3 and 6 months**. i.e Plunket or GP

Date of assessment	
Age at assessment	
Weight in Kg	
Head circumference (cm)	
Length (cm)	
3 month vaccination (if missed on 6 week form)	Yes ☐ No ☐ Date:.....
5 month vaccination	Yes ☐ No ☐ Date:.....
Any concerns about developmental progress requiring medical referral	

***** The Ministry of Health definition for age appropriate vaccination will be used, being receipt of the six-week immunisation within four weeks of due date and within six weeks of due date for the three-month, five-month and 15-month immunisations.

Appendix 8: Monthly surveillance questions for mother and infant

Study Title: Monitoring the safety of pertussis vaccine (Tdap) given during pregnancy

Post-natal survey questions – repeated at monthly intervals until infant 12 months of age. Contact made via e-mail or phone.

1) Has your child been in close contact[1] with anyone with proven pertussis infection?
2) Has your child been in close contact with anyone who has had an unexplained cough lasting > 2 weeks?
3) Has your child had a persistent cough lasting > 10 days?

If the answer to any of these questions is YES the study team will contact the parent to determine if the child has had a significant pertussis exposure or if they child meets the case definition for pertussis. If the child has symptoms they will be invited for a clinical review by a study team doctor at the Paediatric Department, Christchurch Hospital.

[1] Close contact defined as being in the same room as the person for > 1 hour or 5 minutes of face to face contact with a person with proven pertussis who was symptomatic.

	Date contacted	Date replied	Close Contact Pertussis	Close contact cough > 2 weeks	Persistent cough > 10 days	Referred to Study Dr	Swab taken	result
DOB								

Month 1								
Month 2								
Month 3								
Month 4								
Month 5								
Month 6								
Month 7								
Month 8								
Month 9								
Month 10								
Month 11								
Month 12								

[1]

Appendix 9: SAE Reporting Form

Adverse Reactions to Medicines, Vaccines and Devices
and all clinical events for IMMP

PATIENT Details H1574

Surname:	**First Name(s)**	**NHI No:**
		XXX9999
Address:		**Date of Birth:**
		Sex: ☐**M** ☐**F**

ALL MEDICINES IN USE - ASTERISK SUSPECT MEDICINE(S)

Medicine(s) / Vaccine(s)+batch no.	**Daily Dose**	**Route**	**Date Started**	**Date Stopped**	**Reason for Use**

DESCRIPTION OF ADVERSE REACTION

Date of Onset: dd/mm/yy:
Please describe reaction here using as many lines as you need:

Description of Outcome of Adverse Reaction or Incident

Recovered ☐	Not yet recovered ☐	Unknown ☐	Fatal ☐	Date of Death
Severe ? **Yes** ☐	**N**o ☐	**Rechallenge ?** **N**o ☐	**Y**es ☐	Result:

OTHER FACTORS - Please circle

Renal Disease	☐	Hepatic Disease	☐	Allergy ☐	Describe:
OTC Use?	☐	Industrial Chemicals	☐	Other Medical Conditions?	☐

REPORTING DOCTOR/PHARMACIST:

Name:	Telephone:
Address:	
Email address?:	Date:

Post to:	Freepost 112002 The Medical Assessor Centre for Adverse Reactions Monitoring PO Box 913 DUNEDIN	Fax to:	+64-3-479-7150

Appendix 10: SAE with intensity

SERIOUS ADVERSE EVENTS (SAE) (Page 1 of 6)

DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death.

b) is life-threatening.

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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.

c) requires hospitalisation or prolongation of existing hospitalisation.

Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.

When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered 'serious'. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) is a congenital anomaly/birth defect.

f) other.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g) possible drug-induced liver injury

SERIOUS ADVERSE EVENTS (SAE) (Page 2 of 6)
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an SAE, confirm that the following variables are consistent for the SAE which resulted in withdrawal:
  - If investigational product was permanently withdrawn due to an adverse event ...

    •'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event ...

    •'Withdrawal' on the SAE page is recorded as 'Yes'.

    •'Action Taken with Investigational Product(s) as a Result of the SAE' on the SAE page is recorded as 'Investigational Product Withdrawn'.

THE INVESTIGATOR MUST INFORM GSK OF SERIOUS ADVERSE EVENTS BY FAX OR TELEPHONE (FAX PREFERRED) WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT. (The original pages must remain in the Case Report Form/Study File).

SERIOUS ADVERSE EVENTS (SAE) (Page 3 of 6)

INVESTIGATOR INSTRUCTIONS

Diagnosis	Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialled and dated by the investigator. A separate form should be used for each SAE. However, if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page. If this was recorded previously as a non-serious event but has progressed to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
Start Date **Start Time**	Record the start date and time of the first occurrence of the event or signs/symptoms of the serious event, not the date and time the event became serious.
Outcome	All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death.
End Date **End Time**	Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/ Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the SAE.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. Mild = An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. Moderate = An event that is sufficiently discomforting to interfere with everyday activities. Severe = An event that prevents normal everyday activities. Not applicable = Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Action Taken with Investigational Product(s) as a Result of the SAE	Indicate the response to the adverse event, whether it be from the investigator, local physician not in the study, or the subject. Investigational product(s) withdrawn = Administration of investigational product(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more investigational product(s). Dose increased = Dose increased for one or more investigational product(s). Dose not changed = Investigational product(s) continues even though an adverse event has occurred. Dose interrupted/Delayed = Administration of one or more investigational product(s) was temporarily interrupted but then restarted. Not applicable = Subject was not receiving investigational product(s) when the event occurred (e.g., pre-or post-dosing) or the subject died and there was no prior decision to discontinue IP(s).

SERIOUS ADVERSE EVENTS (SAE) (Page 4 of 6)

INVESTIGATOR INSTRUCTIONS

Did the subject withdraw from the study as a result of this SAE	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal from the study, otherwise indicate 'No'.
Relationship to Investigational Product(s)	It is a regulatory requirement for investigators to assess relationship to investigational product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number	

SERIOUS ADVERSE EVENT (SAE)

Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

SECTION 1

Event	**Start Date**	**Start Time**	**Outcome**	**End date**	**End Time**	**Maximum Intensity**	**Action Taken with Investigational Product(s) as a Result of the SAE**	**With-drawal**	**Relationship to Investi-gational Product(s)**
Diagnosis Only (*if known*) Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae 5=Fatal	*If fatal, record date of death.* Day Month Year	Hr : Min 00:00-23:59	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted/ Delayed X=Not applicable	Did the subject withdraw from study as a result of this SAE? Y=Yes[1] N=No	Is there a reasonable possibility the SAE may have been caused by the investi-gational product? Y=Yes N=No
e.g., Anaphylaxis	***25 JAN 03***	***13:25***	***1***	***27 JAN 03***	***10:20***	***1***	***4***	***Y***	***Y***
		:			:				
		:			:				

[1] *Complete Study Conclusion page and ✓Adverse event as reason for withdrawal.*

SECTION 2 Seriousness *(specify reason(s) for considering this a SAE, ✓all that apply:*

[A] ☐ Results in death

[B] ☐ Is life-threatening

[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation

[D] ☐ Results in disability/incapacity

[E] ☐ Congenital anomaly/birth defect

[F] ☐ Other, *specify* _ (*see definition of SAE*)

[G] ☐ Possible drug-induced liver injury (see definition in SAE section of the protocol)

SERIOUS ADVERSE EVENTS (SAE) (Page 5 of 6)

INVESTIGATOR INSTRUCTIONS

SECTION 4 **If Investigational Product was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) Were Administered?**	If deliberate or inadvertent administration of further dose(s) of investigational product(s) to the subject occurred, did the reported adverse event recur?

Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 3 Demography Data

Date of birth ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year Sex ☐ Male ☐ Female Weight ☐☐☐.☐ kg Height ☐☐☐ cm

SECTION 4 If Investigational Product(s) was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) were Administered?

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

SECTION 5 Possible Causes of SAE Other Than Investigational Product(s), ✓*all that apply:*

☐ Disease under study
☐ Medical condition(s) *specify* _____
☐ Lack of efficacy
☐ Withdrawal of investigational product(s)
☐ Concomitant medication(s) *specify* _____
☐ Activity related to study participation *(e.g., procedures)*
☐ Other, *specify* _____

SECTION 6 RELEVANT Medical Conditions

Specify any RELEVANT past or current medical disorders, allergies, surgeries that can help explain the SAE. Ensure each medical condition recorded in this section is also recorded in the appropriate Medical Conditions form.	**Date of Onset** Day Month Year	**Condition Present at Time of the SAE?** Y= Yes N=No	***If No, Date of Last Occurrence*** Day Month Year

SERIOUS ADVERSE EVENTS (SAE) (Page 6 of 6)
INVESTIGATOR INSTRUCTIONS

SECTION 9 **Details of Investigational Product(s)**	Complete this section using the information in the Investigational Product page. Details of all investigational product(s) taken until the time of the SAE should be included. Provide specific details in Section 11 Narrative Remarks if the subject has taken an overdose of investigational product(s), including whether it was accidental or intentional.

Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 7 Other RELEVANT Risk Factors *Provide any family history or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE). Ensure each risk factor recorded in this section is also recorded in the appropriate Medical Conditions form.*

SECTION 8 RELEVANT Concomitant Medications *Include details of any concomitant medication(s) that may help explain the SAE, may have caused the SAE or was used to treat the SAE. Ensure each concomitant medication recorded in this section is also recorded in the Concomitant Medication form.*

Drug Name *(Trade Name preferred)*	**Dose**	**Unit**	**Frequency**	**Route**	**Taken Prior to Study?** Y=Yes N=No	**Start Date** Day Month Year	**Stop Date** Day Month Year	**Ongoing Medication?** Y=Yes N=No	**Reason for Medication**
e.g., Zantac	***150***	***mg***	***BID***	***PO***	***N***	***25 JAN 10***	***27 JAN 10***	***N***	***Gastric ulcer***

SECTION 9 Details of Investigational Product(s)

Was treatment blind broken at investigational site? ☐ Yes ☐ No ☐ Not applicable

Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 10 Details of RELEVANT Assessments *Provide details of any tests or procedures carried out to diagnose or confirm the SAE (e.g., laboratory data with units and normal range) if data for this SAE have not been previously entered, and the CRF includes a page for the test, ensure the data is also entered on the page.*

SECTION 11 Narrative Remarks *(provide a brief narrative description of the SAE and details of treatment given)*

Investigator's signature _
(confirming that the data on the SAE pages are accurate and complete)

Investigator's name (print) _

Date ☐☐ Day ☐☐☐ Month ☐☐ Year