An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Update on Immunization in Pregnancy with Tetanus Toxoid, Reduced Diphtheria Toxoid and Reduced Acellular Pertussis (Tdap) Vaccine

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

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—Public Health Agency of Canada

Également disponible en français sous le titre :
Mise à jour sur l'immunisation durant la grossesse avec le vaccin combiné anti-Tétanos, et à dose réduite contre la diphtérie et la coqueluche acellulaire (dcaT)

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the PHAC Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

1. What

Pertussis caused by *Bordetella pertussis* is an endemic respiratory disease pathogen from which unimmunized infants are at greatest risk of hospitalization and death.

2. Who

This statement addresses maternal[1] Tdap immunization in pregnancy in Canada with the aim of protecting newborn infants in Canada from severe outcomes of pertussis infection.

3. How

Immunization with Tdap vaccine should ideally be provided in every pregnancy between 27 and 32 weeks of gestation. However, Tdap immunization may be provided from 13 weeks up to the time of delivery in view of programmatic and unique patient considerations.

4. Why

Due to high susceptibility to infection, infants who have not initiated vaccination or completed the primary series of pertussis immunization are at highest risk for pertussis complications, including hospitalization and death. Immunization in pregnancy is safe and provides protection to infants until they are able to receive the pertussis vaccine at two months of age.

Due to the varying cycle activity of pertussis in Canada, routine immunization with Tdap vaccine in pregnancy is preferred over its use as an outbreak control measure only. Use of Tdap vaccine during outbreak situations is considered to be logistically challenging and less effective for preventing pertussis in infants compared to routine maternal immunization in pregnancy.

[1] *NACI recognizes that not all people giving birth will identify as women or mothers. For the purposes of this statement, the terms "pregnant woman", "mothers" and "maternal" are used, but should be considered to also apply to those individuals who do not specifically identify as female gender but are the parent gestating the fetus.*

I. INTRODUCTION

In 2013, following an approximately three-fold increase in the number of nationally reported pertussis cases, NACI adopted several recommendations pertaining to the immunization of pregnant women with a tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis (Tdap) vaccine. At the time, based on the reviewed evidence, NACI concluded that vaccination with Tdap vaccine in pregnancy was safe and immunogenic, and recommended that:

- depending on regional epidemiology, immunization with Tdap may be offered during pertussis outbreaks (as defined by a jurisdiction) to pregnant women who are 26 weeks of gestation or greater irrespective of their immunization history, and
- pregnant women who have not been immunized with Tdap in adulthood should be offered a pertussis vaccine.

However, in view of the low number of severe outcomes in newborns being observed in Canada, as well as the uncertainty about the potentially adverse effects of maternally derived antibodies on lowering the infant's response to immunization with diphtheria and tetanus toxoids, acellular pertussis (DTaP) vaccine, routine immunization with Tdap vaccine in pregnancy was not recommended at that time. With the availability of new effectiveness data reported following the implementation of routine maternal immunization programs internationally, the NACI Diphtheria/Tetanus/Pertussis/Polio/Haemophilus Influenza B Working Group (PWG) was again tasked with reviewing the evidence pertaining to the use of Tdap vaccine in pregnancy. In accordance with the direction that was provided by the Canadian Immunization Committee, the objective of this NACI Statement is to provide guidance on maternal immunization in pregnancy as a strategy to reduce disease incidence and severe outcomes (defined as hospitalization or death) from pertussis infection in infants less than 12 months of age.

The specific topics that were reviewed by the PWG included:

- the burden of pertussis in infants less than 12 months of age
- the safety of maternal immunization with Tdap vaccine in pregnancy
- the efficacy and effectiveness of maternal immunization with Tdap in pregnancy in preventing severe outcomes of pertussis infection in infants less than 12 months of age
- the effects of maternal Tdap immunization in pregnancy on an infant's immunological response to the primary vaccine schedule
- the impact of maternal Tdap immunization in pregnancy on long term protection against tetanus, diphtheria and pertussis in children.

II. METHODS

The PWG reviewed evidence on the burden of disease in Canada; vaccine safety and immunogenicity; and vaccine effectiveness in jurisdictions that have implemented maternal immunization programs. The following research questions were developed by the PWG:

- Is there a significant difference in local or systemic adverse events for the mother following immunization with Tdap vaccine in pregnancy (all stages) compared to adult immunization outside pregnancy?

- Is there a significant difference in adverse fetal and neonatal health outcomes for the baby following immunization of their mother with Tdap vaccine in pregnancy?
- Is maternal immunization in pregnancy with Tdap significantly more efficacious or effective in preventing severe disease in infants under 12 months of age compared to no maternal immunization in pregnancy?
- Is the immunogenicity of DTaP vaccination in children born to mothers immunized with Tdap vaccine in pregnancy significantly different compared to infants born to mothers who were not immunized with Tdap vaccine in pregnancy?
- Does maternal immunization with Tdap in pregnancy significantly impact efficacy or effectiveness of DTaP vaccines in preventing related disease in children less than 4 to 6 years of age?

In addition to the review of unpublished data, including current international practices, a literature search and review of articles published until November 28, 2016 was conducted and updated to July 25, 2017. A total of 59 articles were identified, retrieved and included in the literature review to inform this statement. NACI and PWG members also reviewed the immunogenicity and safety data from one unpublished Canadian clinical trial (NCT00553228), which were found to be consistent with the results from other published RCTs. A detailed analysis of the relevant studies is presented in the NACI *Literature Review on Immunization in Pregnancy with Tetanus Toxoid, Reduced Diphtheria Toxoid and Reduced Acellular Pertussis (Tdap) Vaccine: Safety, Immunogenicity and Effectiveness*.

Epidemiological analysis was conducted using national surveillance data including the Canadian Notifiable Disease Surveillance System (CNDSS), the Immunization Monitoring Program Active (IMPACT) and the Canadian Institute for Health Information Discharge Abstract Database (DAD). These data are subject to limitations such as changes in reporting practices over time, number of participating institutions as well as changes in methods for laboratory detection of pertussis cases.[1-3] In general, due to the limitations of existing surveillance systems, surveillance data tend to underestimate the true number of pertussis cases.

The knowledge synthesis was performed by two technical advisors at PHAC, and supervised by the PWG. Following the critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy were prepared, and proposed recommendations for vaccine use were developed.

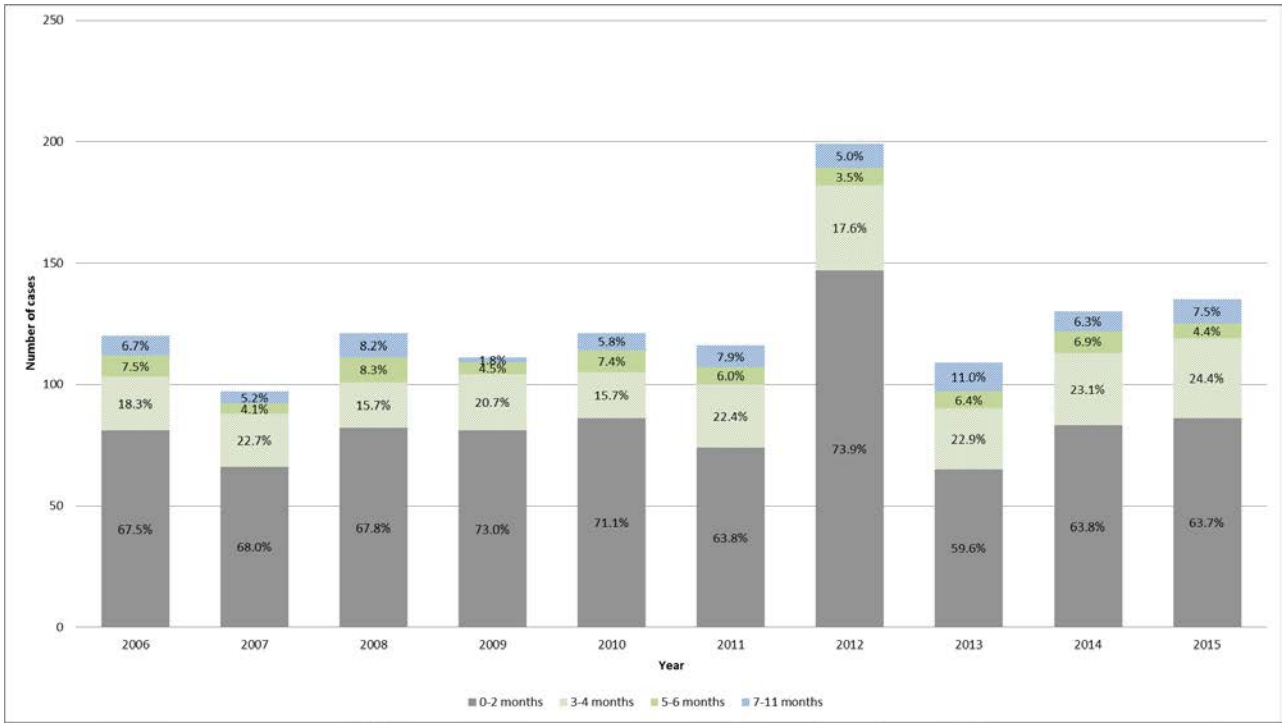
These data tables are available in NACI's *Literature Review on Immunization in Pregnancy with Tetanus Toxoid, Reduced Diphtheria Toxoid and Reduced Acellular Pertussis (Tdap) Vaccine: Safety, Immunogenicity and Effectiveness.*

The PWG Chair presented the evidence and proposed recommendations to NACI at its meeting on June 7, 2017. Following the comprehensive evidence review and consultations, NACI voted on specific recommendations on September 27, 2017. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text below.

III. EPIDEMIOLOGY

In Canada, pertussis is an endemic and cyclical disease. Pertussis peaks occur at two- to five-year intervals, with cycle activity varying by region.[4, 5] Since the routine use of acellular pertussis vaccine in 1997/1998, there had been an overall decline in the incidence rate of pertussis until 2011.[4]Between 2012 and 2015, increased annual incidence rates were observed, ranging from 3.6 to 13.4 cases per 100,000 population.[6] The incidence peaks in 2012 and 2015 were associated with numerous outbreaks that occurred across Canada.[4, 7-10]

Figure 1. Annual number of reported pertussis cases in infants less than one year old in Canada by age in months, 2006-2015



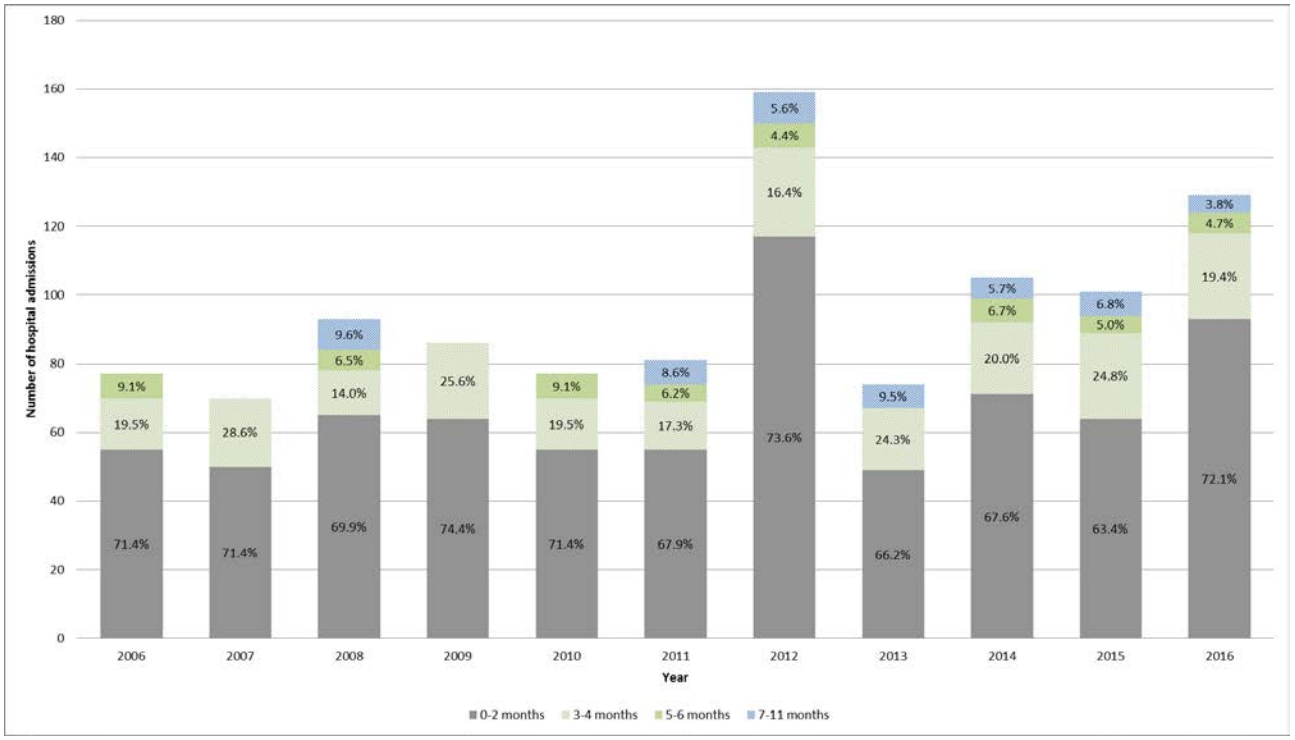
*Data were obtained from the Canadian National Notifiable Disease Surveillance System (CNDSS).

†Case data from were obtained from CNDSS. Case-level data were available for BC, AB, SK, ON, QC, PE (2010-2015), YK, and NU. Data were not available for MB, NL, NB, NS, PE, and NT (2006-2009),

Pertussis incidence varies by age group, with the greatest risk of infection and associated complications in unvaccinated or under vaccinated infants.[4-6, 10-12] Between 2006 to 2015, the average age-specific incidence rates reported through CNDSS were highest among infants less than one year of age at 71.2 cases per 100,000 population, followed by children one to nine years of age (43.0 cases per 100,000), and children ten to 19 years of age (26.1 cases per 100,000). As shown in **Figure 1**, the majority of reported cases of pertussis between 2006 and 2015 were reported in infants less than two months of age (range 60% to 74%) followed by infants three to four months of age (range 16% to 24%). A sharp increase in the number of cases was reported in 2012 in infants less than two months of age.

Pertussis-related hospitalization data reported through DAD based on primary diagnosis demonstrate that hospitalizations and admission to special care units (SCU) are disproportionately greatest in infants under one year of age.[4, 5, 12] From 2006 to 2015, the hospitalization rates associated with pertussis were 33.6 per 100,000 population in infants under one year of age and less than one per 100,000 population in other age groups. As shown in **Figure 2**, the majority of the hospitalized infants were less than two months of age (range 63% to 74%), followed by three to four months of age (range 16% to 29%). Overall, the majority of SCU admissions reported in DAD were in infants under the age of one year (320/384). Between 2006 and 2016, infants less than two months of age accounted for the largest proportion of SCU admissions (40.5%), followed by infants three to four months of age (21.4%). Similar to the pertussis incidence trend, a sharp increase in the number of hospitalization for infants under two months of age was reported in 2012.

Figure 2. Annual number of pertussis hospitalizations in infants less than one year old in Canada, by age in months*‡, 2006 to 2016.[5, 6, 12]



*Annual counts of hospitalizations less than five per age category were supressed from the figure due to privacy issues.

‡Hospitalization data were acquired from the Canadian Institute for Health Information's Discharge Abstract Database. Hospitalization data from Quebec for 2011 to 2015 were not available for this analysis.

Lack of maternal immunity is assumed to increase infant's susceptibility to infection both by increasing the risk of disease in mothers (and subsequent transmission to the infant) and by not providing sufficient passive protection through antibody transfer (via the placenta or via breast milk). A recent cohort serosurvey has shown that the majority of pregnant women in Canada had undetectable anti-pertussis toxin levels.[13, 14] While no serologic correlate of clinical protection against pertussis currently exists, this likely indicates that i) a high proportion of pregnant women in Canada are susceptible to pertussis and ii) mothers would be unable to passively transfer pertussis-associated antibodies to newborn infants, rendering them susceptible until they start to

become protected through vaccination at two months of age.[13-19] Parents (primarily mothers) and siblings are considered to be the most important source of pertussis transmission to young infants[20-33].

According to the national survey on adult immunization[34] (all adults 18 years of age and older), only 9.3% (95% CI, 8.1-10.5) reported having received at least one dose of acellular pertussis-containing vaccine since their 18th birthday. Considering the lack of Tdap coverage data in pregnancy due to the absence of routine maternal immunization programs in Canada, the PWG reviewed information on influenza immunization in pregnancy. A cohort study[35] that assessed influenza vaccination in pregnancy from 1990 to 2002 in NS estimated that 2.6% of all pregnant women and 6.7% of pregnant women with comorbidities received immunization. A retrospective population-based cohort study in ON from 2009 to 2010 estimated that 42.6% of women had received influenza immunization during pregnancy during the H1N1 pandemic season. In Canada, the mean age of first time mothers is 30 years, with approximately 380,000 live births annually reported since 2010.[36, 37]A recently conducted internal survey of provincial and territorial (P/T) immunization practices (unpublished) indicates that the implementation of maternal Tdap immunization programs according to 2014 NACI recommendations has been only sporadically carried out, depending on the intensity and stage of the outbreak. Logistical challenges of providing vaccination in a timely manner were cited as being a major obstacle for successful program implementation.

Additional details on the overall epidemiology of pertussis and Tdap immunization coverage in Canada are available on the Government of Canada Immunization and vaccines webpage. (https://www.canada.ca/en/public-health/topics/immunization-vaccines.html)

An environmental scan of international practices identified several jurisdictions where maternal Tdap immunization programs in pregnancy are currently in place. In the majority of jurisdictions these programs were implemented as part of an outbreak management strategy with a goal of reducing an increase in disease incidence rates and deaths in the less than one-year age group. Since then, in many of these countries including the US, UK, Ireland, Spain, Belgium, Switzerland, Greece, Argentina, Brazil, Colombia, Mexico and Israel, ongoing maternal Tdap immunization in pregnancy has been incorporated into routine adult immunization programs. Although the environmental scan did not identify any program evaluation reports, a detailed update on the UK maternal immunization program that was provided by Public Health England suggested a 90% effectiveness of the national program in preventing laboratory confirmed disease (95% in preventing death) in infants less than 2 months of age.[38-41]

IV. VACCINE

IV.1 Adult pertussis vaccine preparations authorized for use in Canada

Table 1. Contents of adult pertussis vaccine preparations authorized for use in Canada*

Vaccine Ingredients	Adacel®, Sanofi[42]	Boostrix®, GSK[43]
Pertussis Toxin (PT, µg)	2.5	8
Pertussis filamentous hemagglutinin (FHA, µg)	5	8
Pertussis pertactin (PRN, µg)	3	2.5
Pertussis fimbriae (FIM 2/3, µg)	5	-
Diphtheria Antigen (Lf µg)	2	2.5
Tetanus Antigen (Lf, µg)	5	5
Aluminum Adjuvant (mg)	1.5	0.5
Other ingredients	2-phenoxyethanol, water	sodium chloride, water
Trace Amounts	formaldehyde, glutaraldehyde	

*Inactivated poliomyelitis vaccine (IPV) containing vaccine preparation also available (eg Adacel-Polio, Boostrix-Polio).

Based on the available trial data at the time of authorisation, none of the adult vaccine formulations have been explicitly indicated for use in pregnancy. However, according to the current product monographs, none of the adult formulations authorized for use in Canada are contraindicated for use in pregnancy.

IV.2 Immunogenicity

During pregnancy, maternal IgG antibodies are transported across the placenta into fetal circulation, with active antibody transport increasing via the neonatal Fc receptor over the third trimester. Antibody levels to different pertussis antigens following maternal immunization have been reported for pregnant women and their infants prior to and following the receipt of infant DTaP-containing vaccines. When interpreting the results of these studies, it should be noted that a defined correlate of protection against pertussis infection remains to be determined.

IV.2.1 Immunogenicity for the mother during pregnancy

The literature review conducted by NACI identified fourteen relevant immunogenicity studies, four of which were RCTs. In all RCTs immune response was measured following the administration of Tdap in the third trimester of pregnancy. Compared to placebo (0.9% saline or TT), in all studies immunization increased maternal anti-PT levels at least 4-fold, while other vaccine-contained antigens increased more than 10-fold[44-46]. In RCTs that compared immune responses between women receiving Tdap during and outside of pregnancy, there were no significant differences in antibody levels. In these studies, although suppressed cellular immunity in pregnant women was noted, there were no observed differences in cellular response one year after immunization.

Other clinical and observational studies that assessed antibody responses to Tdap immunization in pregnancy reported results that were consistent with those reported in RCTs.[44-46] In the majority of reviewed studies, post immunization increases in antibody levels resulted in more than 90% of women achieving anti-PT levels ≥10 IU/ml one month following immunization.[47-49] In reviewed studies that assessed antibody persistence after immunization in pregnancy, significant decreases were observed for all pertussis antibody levels, with anti-PT concentrations declining by half, one year after immunization.[50, 51] Studies that measured antibody concentrations in colostrum and breast milk following maternal immunization in pregnancy found only modest increases in IgA and IgG anti-PT and anti-FHA levels compared to women not immunized in pregnancy.[52, 53] However, antibody levels in these studies remained detectable until at least 8 weeks after delivery, suggesting that breastfed infants could additionally benefit from the protection afforded by antibodies in breast milk.

IV.2.2 Maternally derived antibody levels in infants prior to the infant receipt of DTaP

Twenty one relevant studies were identified in the literature search, of which four were RCTs that reported results on maternal antibody levels in term infants. All studies provided evidence of efficient transplacental transfer of all vaccine-contained antibodies to the fetus prior to delivery.

While rapid waning of maternal antibodies within two months of birth was evident in all trials, infants born to mothers that received Tdap maintained significantly higher antibody levels compared to those observed in the control groups.[44-46, 54] These findings were also confirmed in all the reviewed observational studies.[41, 55-59] Additionally, smaller serological studies published to date suggest that maternal immunization in pregnancy does not seem to affect the selective transfer of high avidity and function-specific antibodies that can effectively stimulate infant innate immune responses (i.e. phagocytic activity of NK cells).[60-62] One study also found increased efficiency of placental antibody transfer in mothers who were immunized with Tdap compared to those who did not receive the vaccine in pregnancy.[63] With the exception of one small observational study, maternal immunization with Tdap in pregnancy was found to be more immunogenic when provided earlier in pregnancy, but after 13 weeks of gestation. [64] Compared to 31 to 36 weeks of gestation, immunization at 27 to 30 weeks of gestation was found to result in higher cord to maternal antibody ratios and anti-PT relative avidity index, with umbilical cord anti-PT avidity maturation linearly increasing with time to delivery.[65]Higher cord antibody levels (anti-PRN and anti-PT) were also reported when mothers received Tdap between 28 and 32 weeks of gestation compared to 33 to 36 weeks of gestation, and at 13 to 25 weeks of gestation when compared to immunization between 26 and 36 weeks of gestation.[66, 67] Two studies that measured anti-PT concentrations at birth following maternal immunization at less than 26 weeks of gestation, found antibody levels above 10 EU/ml to be present in over 90% of infants.[49, 67]

In studies that measured pertussis antibody levels in preterm infants, immunization during the second trimester resulted in higher concentrations as well as higher proportion of infants achieving anti-PT levels above 5 EU/ml compared to those whose mothers were immunized in the third trimester.[68, 69] In one study that assessed the effects of pregnancy body weight on neonatal antibody levels, no statistically significant differences in antibody concentrations were found between infants born to mothers with normal, overweight or obese body mass index (BMI) measurements.[70]

IV.2.3 Immunogenicity of DTaP in infants born to women immunized with Tdap in pregnancy

Five RCTs measured immunological responses in infants following DTaP administration. In all trials, antibody levels against all pertussis antigens were lower in infants whose mothers received Tdap in the third trimester of pregnancy than those in the control group. These differences were observed after 2nd or 3rd DTaP dose, with the cross-over in antibody concentrations occurring between 4 and 6 months of age. [41, 47, 55, 56, 62, 68] In the majority of reviewed RCTs and observational studies, statistically significant differences in antibody levels and avidity disappeared with the receipt of the booster (fourth) DTaP dose after 15 months of age.[41, 47, 55, 56, 62, 68] Impact of maternal Tdap immunization in pregnancy on infant response to other vaccine contained antigens was measured in four studies.[41, 45, 56, 71] While enhanced immunological response to tetanus and tetanus conjugated vaccines and reduced immunological response to diphtheria and CRM-conjugated vaccines (e.g. meningococcal, pneumococcal vaccines) was noted by several research groups, the clinical impact of these findings was not assessed in the reviewed literature. Given the lack of long-term data, the relevancy of these findings to existing immunization programs therefore remains unknown.[71, 72]

IV.3 Effectiveness of maternal Tdap immunization during pregnancy for preventing pertussis in infants

All studies in which effectiveness of maternal immunization in pregnancy was estimated consistently showed high protection against pertussis in infants less than 3 months of age. The majority of studies identified through the literature review originated from the UK, in which a national maternal immunization program has been implemented since October 2012.[38-40] In infants less than 2 months of age, vaccine effectiveness was estimated to be over 90%, with no death observed among infants whose mothers received Tdap prior to 36 weeks of pregnancy.

Vaccine effectiveness was also reported to persist after the receipt of the first three DTaP doses, with immunization in pregnancy resulting in additional protection of up to 70% in children whose mothers received Tdap in pregnancy. Similar results were subsequently reported in studies conducted in the United States of America (US) and Spain.[73-75] In one US study that assessed effectiveness of maternal immunization in relation to hospitalization outcomes, infants whose mothers were immunized with Tdap were more likely to have a milder disease course and be older when they developed pertussis, as well as be less likely to have the classic symptoms of pertussis (i.e. paroxysmal cough, apnea, cyanosis).[73] In another US study, a significantly lower risk of hospitalization and ICU admission was also observed in infants whose mothers received Tdap.[74] In the only study which used surveillance data to estimate maternal Tdap program effectiveness that was conducted in Argentina, significantly lower incidence was observed among infants in parts of the country in which maternal immunization coverage was over 50% compared to those in which coverage was lower.[76, 77]

IV.4 Adverse Events

In total, 16 studies reported on local and systemic adverse events in mothers following Tdap vaccination in pregnancy and 24 studies included data on pregnancy complications or adverse fetal, neonatal or infant outcomes. In addition, the PWG was made aware of the US Vaccine Adverse Event Reporting System (VAERS) data that was presented to ACIP at its meeting in June 2016. Altogether, ten years of passively reported VAERS data and eight years of actively reported longitudinal US Vaccine Safety Datalink (VSD) data have been reported in peer-reviewed publications.

IV.4.1 Maternal local and systemic adverse events

In four RCTs that reported on the safety of Tdap in pregnancy, no differences in reporting any injection site or systemic reactions were observed independent of the vaccine used in the control group (placebo or tetanus toxoid).[44-46] These trials also did not report serious adverse events related to vaccination. This was consistent with the findings of studies that described immunization outcomes following the implementation of national maternal Tdap immunization programs. The most common AEs reported through the VAERS (passive surveillance system) between November 2011 and June 2016, included local (i.e. injection site reactions or extremity myalgia) and systemic events (fever, chills and headache) associated with Tdap immunization.[78-80] An analysis of VSD (active surveillance system) data found similar results, with no increased risk determined for neurologic events, incident gestational diabetes, thrombocytopenia, venous thromboembolism or cardiac events (myocarditis, pericarditis, cardiomyopathy, heart failure).[81, 82] There were also no differences found in the frequency of fever, allergic reactions or local reactions between women who received Tdap vaccine at less than 2 years compared to more than 5 years after their last dose of a tetanus-containing vaccine. In Argentina, no serious or fatal events were reported during the two years of national maternal immunization program implementation.[76]

In published observational studies, results differed according to study location, design and size. In a study that was conducted in Australia local reactions were more frequently reported in pregnant women receiving Tdap alone compared to influenza vaccine alone or together with Tdap.[83] A similar study conducted in New Zealand that assessed outcomes of Tdap vaccination with or without influenza vaccine reported high rates of injection site pain (80%).[84] Neither of these studies found SAEs to be caused by Tdap vaccination. Similar results were reported in a study that was conducted in Belgium in which stiffness of the arm at the injection site was reported by 74% of study participants, but SAEs were not found to be related to vaccination.[55] A study conducted in the US that compared Tdap immunization during and outside pregnancy, found the rates of moderate to severe injection site pain and malaise to be higher in pregnancy, while rates of fever, headaches, injection site swelling and redness were similar between the two study groups.[85]

IV.4.2 Pregnancy-related adverse events

In an analysis of VAERS (passive surveillance system) data, less than 15 events (each) of spontaneous abortion, premature delivery at less than 37 weeks of gestation, stillbirth, choriomanionitis and oligohydroamnios were reported between 2005 and 2016.[78-80, 86] Approximately half of the event submissions to VAERS were made by the two Tdap vaccine manufacturers, which collected this information through their product-specific pregnancy registries.[87] An analysis of VSD (active surveillance system) data provided similar findings, with the exception of chorioamnionitis, for which a small but statistically significant increased relative risk (adjusted rate ratio 1.23 [95% CI: 1.17-1.28]) was reported.[82, 88-90] However, a subsequent

analysis of this data did not find any increased risks for infant clinical outcomes considered to be associated with chorioamnionitis. In addition, no associations were found between adverse birth outcomes and gestational age at time of Tdap vaccination or timing since prior TT vaccination.[82, 89] A small increased risk of chorioamnionitis (relative risk of 1.11 [95% CI: 1.07–1.15]) and postpartum hemorrhage (relative risk of 1.23 [95% CI: 1.18–1.28]) has also been reported following an analysis of commercial insurance claim data of over 207,000 women of whom approximately 150,000 received Tdap during pregnancy.[91]

In the UK, an analysis of CPRD (active surveillance system) data in the first six months of national program implementation found stillbirth rates in women immunized with Tdap in pregnancy to be similar to the estimated national stillbirth rate.[92] During this time there were no reported cases of placental abruption or vasa previa after vaccination, and no significant differences were reported in the time to delivery and median birth weight between the vaccinated and unvaccinated women.

In RCTs, no differences in the frequency of adverse outcomes in women who received Tdap in pregnancy and women who received placebo (0.9% saline or TT) were reported.[44-46] Pregnancy outcomes captured in EMR data that were evaluated in observational studies, similarly, did not show higher frequencies of chorioamnionitis or stillbirth rates in pregnancies in which mothers received one or more doses of Tdap vaccine.[47, 55, 93-97] In cohort studies that evaluated pregnancy and infant outcomes without a comparator group, none of the serious adverse events in pregnancy were found to be caused by Tdap vaccination.[84, 98, 99]

The PWG was also provided with an analysis of Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) safety data. Between 2007 and 2016, only 8 pregnancy or pregnancy-related events following immunization with Adacel™ (4 reports) or Boostrix™ (4 reports) provided alone or concomitantly with TIV (2 reports) were identified, all considered to be mild or non-related to immunization. These included vaccination site reaction (3 cases), localized or generalized rash (3 cases) and gastrointestinal symptoms (2 cases). Among these, 4 reports included maternal outcomes (2 fully recovered and 2 not yet recovered at time of reporting) and 5 reported on maternal care utilization (2 sought medical care from primary care physician, 1 ER consultation and in 1 case, no further medical care was sought).

IV.4.3 Fetal and neonatal adverse events

In the US, studies in which VAERS and VSD surveillance system data was reviewed for adverse birth outcomes found a low number of these events occurring in infants whose mothers received Tdap in pregnancy.[78-80, 86] Between 2005 and 2016 only 1% (n=4) of VAERS reports included a major birth defect, while an analysis of VSD data that included pregnancy outcomes from over 197,000 pregnancies did not find an increased risk for infant clinical outcomes that are associated with maternal chorioamnionitis (i.e. newborn transient tachypnea, neonatal sepsis, neonatal pneumonia, respiratory distress syndrome and newborn convulsions). Analysis of VSD data that compared safety outcomes of maternal Tdap vaccination relative to influenza immunization in pregnancy did not find increased risks for microcephaly, preterm delivery, low birth weight and SGA.[82, 88] In the UK, a study that reported on the national surveillance system data (CPRD) in the first six months of national maternal Tdap program implementation found no cases of fetal distress or child renal failure.[92] An analysis of Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) data from 2007 to 2016 identified the only pregnancy outcome associated with immunization in pregnancy as being a case of a spontaneous abortion in a blighted ovum case.

In RCTs, no differences in the frequency of adverse neonatal outcomes including infants' gestational age, birth weight, Apgar scores, neonatal examination or complications, as well as differences in the infants' growth and development up to 13 months of age were found between women who received Tdap in pregnancy and women who received placebo (0.9% saline or TT).[44-46] Similarly, none of the reviewed observational studies that analyzed medical records for AEs post maternal Tdap immunization in pregnancy found increased frequencies in birth defects or differences in 5-minute Apgar scores, cord blood pH values or other adverse birth outcome indicators.[47, 55, 93-97] In one study that evaluated hospitalization and other outcomes of children up to 16 months of age, no differences in adverse outcomes were observed based on maternal immunization status, except for low birth weight and NICU admissions (particularly due to preterm birth and anemia) that were more frequently reported in the group of infants whose mothers did not receive Tdap in pregnancy.[100] None of the cohort studies that evaluated infant outcomes without a comparator group reported adverse infant outcomes.[84, 98, 99]

Although no major safety issues have been detected in the reviewed literature, it should be noted that none of the reviewed studies were sufficiently powered to detect small risk differences. This is particularly relevant to outcomes of interest that are frequent among non-vaccinated individuals (e.g. low birth weight, preterm birth or miscarriage) in which case detection of rare vaccine-associated risks requires well powered trials involving large populations or robust post marketing surveillance data.[101]

V. RECOMMENDATIONS

Following the thorough review of available evidence, NACI issued the following recommendation. In adopting this recommendation and for the purposes of publicly funded program implementation, P/Ts may consider economic factors and other local operational factors. NACI will continue to carefully monitor the scientific developments related to maternal pertussis immunization in pregnancy and will update recommendations as evidence evolves.

Recommendation: NACI recommends that immunization with Tdap vaccine should be offered in every pregnancy, irrespective of previous Tdap immunization history (Strong NACI Recommendation). NACI concludes that there is good evidence to recommend immunization (Grade A Evidence)

Routine maternal Tdap immunization during pregnancy will provide a more robust and complete protection against pertussis in infants compared to immunization during outbreak settings only.

Tdap immunization in pregnancy has been shown to protect 9 of 10 infants against pertussis less than 3 months of age. No significant safety issues have been detected in the currently available body of scientific literature and no increased risk of serious adverse pregnancy, maternal or infant events have been reported in countries that are routinely offering Tdap vaccine for immunization in pregnancy. Similarly, no serious adverse events have been detected in Canada through CAEFIS. There is currently no indication of a clinically significant change in the priming of the immunological memory of infants exposed to higher maternally derived antibody concentrations following Tdap vaccination in pregnancy. Given the rapid waning of maternal antibody observed in studies, vaccination should be offered in each pregnancy irrespective of immunization history or the interval between pregnancies.

- **NACI recommends that immunization with Tdap vaccine should ideally be provided between 27 and 32 weeks of gestation (Strong NACI Recommendation, Grade A Evidence). Evidence also supports providing maternal Tdap over a wider range of gestational ages, and NACI recommends that it may be provided from 13 weeks up to the time of delivery in view of programmatic and unique patient considerations (Discretionary NACI Recommendation, Grade A/B Evidence).**

Immunization should ideally be offered at 27-32 weeks of gestation, which is supported by the strongest safety and effectiveness data. Immunization between 13 and 26 weeks of gestation may also be considered in some situations (e.g. pregnancies with an increased risk of preterm delivery) to allow for longer placental exposure to higher antibody levels and maximization of antibody transfer. While it is preferable that immunization is administered in sufficient time before birth (i.e. 4 weeks) to allow optimal transfer of antibodies and direct protection of the infant against pertussis, it should be considered until the end of pregnancy, as it has the potential to provide partial protection. If Tdap immunization was provided early in pregnancy (e.g. prior to recognition of pregnancy), it is not necessary to re-immunize after 13 weeks of gestation.

Table 2. MANAGEMENT OPTIONS

Various options for timing of pertussis immunization are provided, and the decision on which option is preferable may depend on the considerations itemized in the table below:

Options	Considerations	Decision Points
1. Immunization at 27-32 weeks of gestation	**Safety** • Strong safety data in third trimester **Effectiveness** • Effectiveness data primarily span vaccination at 27-36 weeks of gestation. **Immunogenicity** • Peak maternal anti-pertussis antibody levels are achieved approximately 4 weeks following vaccination • Placental transfer of maternal antibodies is optimal in third trimester **Feasibility or Acceptability** • Could be paired with routine prenatal visit during which	Optimal balance between safety data, clinical opportunities, limited antibody waning potential, efficient antibody formation and placental transfer for term pregnancies. This option is supported by the strongest safety and effectiveness data of all the options, and allows enough time for the antibody response to fully develop in pregnancy. Vaccination can be paired with routine maternal visits, but may not provide protection for some preterm births.

	gestational diabetes screening is offered (24-28 weeks of gestation)	
2. Immunization at 13-26 weeks of gestation	**Safety** • Fewer safety data in second trimester **Effectiveness** • Effectiveness data not stratified for immunization in second trimester (includes immunization in both second and third trimester). **Immunogenicity** • Peak maternal anti-pertussis antibody levels are achieved approximately 4 weeks following vaccination • Some reports have shown greater antibody concentrations in infants following vaccination at 13-25 weeks compared to ≥26 weeks • Earlier vaccine administration in second trimester has been shown to result in higher antibody avidity (binding) **Feasibility or Acceptability** • Could be paired with routine prenatal visits, either after detailed anatomical ultrasound is reviewed (typically done between 18-22 weeks of gestation) or when gestational diabetes screening is performed (24-28 weeks of gestation)	Safety data are fewer for second trimester, and effectiveness data are not stratified for immunization during second trimester. Second trimester vaccination increases clinical opportunities to offer vaccination and ensures optimal antibody formation and transfer for both term and preterm infants. For preterm deliveries, a narrow window of opportunity exists between onset of transplacental antibody transfer at 20 weeks and delivery
3. Immunization before 13 weeks of gestation	**Safety** • Limited safety data in first	Safety data are limited before 13 weeks, and effectiveness data are not stratified for first trimester

	trimester **Effectiveness** • No effectiveness data stratified for immunization prior to 13 weeks of gestation **Immunogenicity** • Maternal antibodies will start to wane prior to term delivery • Placental transfer of maternal antibodies is minimal prior to third trimester **Feasibility or Acceptability** • If vaccine is administered prior to detailed anatomical ultrasound, fetal anomalies and other first trimester pregnancy-related complications may be misattributed to the vaccine • The vaccine may not be considered acceptable by patients and clinicians in the first trimester of pregnancy	immunization. When given early in pregnancy antibody may wane before term delivery There is a risk of adverse events in pregnancy being misattributed to vaccination.
4. Immunization after 32 weeks of gestation	**Safety** • Strong safety data in third trimester **Effectiveness** • Effectiveness data primarily span vaccination at 27-36 weeks of gestation. **Immunogenicity** • Placental transfer of maternal antibodies is optimal in third trimester. • Peak maternal anti-pertussis antibody levels are achieved approximately 4 weeks	The strongest safety and effectiveness data are from the third trimester. This option may not allow sufficient time (i.e. 4 weeks) for the development and transfer of maternal antibodies before delivery. Late immunization will not provide protection for most preterm births. There may be fewer clinical opportunities to offer vaccination in late pregnancy compared to earlier vaccination.

	following vaccination. **Feasibility or Acceptability** • Clinical opportunities for vaccination exist with frequent routine prenatal visits towards the end of pregnancy.	

VI. RESEARCH AND EVALUATION PRIORITIES

Based on the experience of maternal influenza immunization in pregnancy, the large numbers needed to detect rare outcomes and the potential for maternal pertussis vaccination in pregnancy to affect overall pertussis control in the longer term, further research and evaluation is strongly recommended and should be funded as part of any new program. Research to address the following outstanding questions related to immunization in pregnancy is encouraged:

- further work on determining the long-term impact of maternal vaccination in pregnancy on vaccine effectiveness in children and adults (e.g. long-term effect on disease epidemiology as a result of lower infant antibody levels);
- surveillance on mother-infant dyads that have received vaccine;
- safety and impact of repeated Tdap in subsequent pregnancies;
- safety of immunization earlier in pregnancy;
- optimal timing for Tdap administration, resulting in optimal transplacental antibody transfer and infant protection;
- cost-effectiveness of maternal pertussis immunization during pregnancy in the Canadian context;
- the impact of mothers' own childhood primary immunization series with either whole cell versus acellular pertussis;
- development of more effective infant pertussis vaccines.

Implementation research and evaluation is needed to identify the best settings for delivery of vaccine to optimize uptake and determine how to overcome any health care system barriers or acceptability barriers to achieving good coverage.

Additional research pertaining to broader knowledge gaps concerning immunization against pertussis is required to complement research related to immunization in pregnancy. Areas of particular interest include:

- determination of correlates of protection
- impact on infant responses to and protection from vaccines conjugated with TT- and CRM-carrier proteins (e.g. pneumococcal)

VII. SURVEILLANCE AND MONITORING ISSUES

Pertussis has been a nationally reported disease since 1924. Ongoing and systematic data collection, analysis, interpretation and timely dissemination is fundamental to planning, implementation, evaluation, and evidence-based decision-making. To support such efforts, NACI encourages surveillance improvements in the following areas:

- improved data quality, including completeness of information particularly immunization status;
- enhanced pertussis surveillance to detect outbreaks quickly and understand the burden of disease in different age groups;
- disease surveillance to determine the impact of changing immunization programs, with particular focus on invasive pneumococcal disease (IPD)
- investigating the use of a case definition that allows for milder cases of pertussis.[102];
- active safety evaluation and surveillance including use of linked administrative data
- monitoring the occurrence of rare safety events following maternal vaccination in pregnancy through long-term follow up of large cohorts;
- improving methods of assessing vaccine coverage including developing methods to monitor coverage of maternal immunization in pregnancy (ideally through comprehensive immunization registries);
- improving collaboration between public health and industry in Canada and internationally on monitoring disease activity, vaccine safety and program outcomes.

TABLES

A detailed analysis of the relevant studies, including evidence tables with quality appraisal for individual studies, is presented in the NACI *Literature Review on Immunization in Pregnancy with Tetanus Toxoid, Reduced Diphtheria Toxoid and Reduced Acellular Pertussis (Tdap) Vaccine: Safety, Immunogenicity and Effectiveness.*

Table 3. Ranking Individual Studies: Levels of Evidence Based on Research Design

Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 4. Ranking Individual Studies: Quality (internal validity) Rating of Evidence

Quality Rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

Table 5. NACI Recommendations: Strength of Recommendation and Strength of Evidence

STRENGTH OF NACI RECOMMENDATION	STRENGTH OF EVIDENCE
Based on factors not isolated to strength of evidence (e.g. public health need)	***Based on assessment of the body of evidence***
Strong "*should/should not be* offered" ➢ Known advantages outweigh known disadvantages ("should"), OR known disadvantages outweigh known advantages ("should not") ➢ Implication: A strong recommendation applies to most populations/patients and should be followed unless a clear and compelling rationale for an alternative approach is present	A - *good evidence* to recommend
	B – *fair evidence* to recommend
	C – *conflicting evidence*, however other factors may influence decision-making
	D – *fair evidence* to recommend against
	E – *good evidence* to recommend against
	I – *insufficient evidence* (in quality or quantity), however other factors may influence decision-making
Discretionary "*may be* considered" ➢ Known advantages closely balanced with known disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists ➢ Implication: A discretionary recommendation may be considered for some populations/patients in some circumstances. Alternative approaches may be reasonable.	A - *good evidence* to recommend
	B – *fair evidence* to recommend
	C – *conflicting evidence*, however other factors may influence decision-making
	D – *fair evidence* to recommend against
	E – *good evidence* to recommend against
	I – *insufficient evidence* (in quality or quantity), however other factors may influence decision-making

LIST OF ABBREVIATIONS

Abbreviation	***Term***
ACIP	Advisory Committee on Immunization Practices (US)
BSA	Bovine Serum Albumin
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CDC	Centers for Disease Control and Prevention (US)
CI	Confidence intervals
CIG	Canadian Immunization Guide
CNDSS	Canadian Notifiable Disease Surveillance System
CPRD	Clinical Practice Research Database (UK)
DAD	Discharge Abstract Database
DIP	Diphteria toxin/toxoid
DTaP	Diphtheria and tetanus toxoids, acellular pertussis vaccine
DTwP	Diphtheria and tetanus toxoids, whole cell pertussis vaccine
EU	Endotoxin Unit
FHA	Pertussis filamentous hemagglutinin
FIM	Fimbriae
FIM 2/3	Pertussis fimbriae
IMPACT	Immunization Monitoring Program Active
JCVI	Joint Committee on Vaccination and Immunization (UK)
Lf	Limit of flocculation
LPF	Lymphocyte proliferating factor
PHAC	Public Health Agency of Canada
PRN	Pertactin
PT	Pertussis Toxin
PWG	NACI Diphtheria/Tetanus/ Pertussis/Polio/Haemophilus Influenza B Working Group
RCT	Randomized Controlled Trial
SGA	Small for gestational age
Tdap	Tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine
TT	Tetanus toxin
The Agency	Public Health Agency of Canada
µg	Microgram
VAERS	Vaccine Adverse Event Reporting (US)
VE	Vaccine effectiveness
VPD	Vaccine-Preventable Diseases
WHO	World Health Organization

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