

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

Update on Pertussis Vaccination in Pregnancy

PROTECTING CANADIANS FROM ILLNESS



Public Health
Agency of Canada

Agence de la santé
publique du Canada

Canada

**TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP,
INNOVATION AND ACTION IN PUBLIC HEALTH.**

—Public Health Agency of Canada

Également disponible en français sous le titre :
Mise à jour sur la vaccination contre la coqueluche pendant la grossesse

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Publication date: February 2014

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Cat.: HP40-93/2014E-PDF
ISBN: 978-1-100-23146-4
Pub.: 130534

PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency 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 Agency's 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 table highlights key information for immunization providers. Please refer to the remainder of the Statement for details

| | |
|----------------|---|
| 1. What | <i>Bordetella pertussis</i> is a respiratory pathogen which has the heaviest burden of mortality and morbidity in the first 6 months of life. In Canada, we have seen an increase in the total number of cases of pertussis reported nationally in 2012. |
| 2. Who | In order to protect newborn infants against pertussis, this statement addresses pregnant women who are 26 weeks of gestation or greater. |
| 3. How | <p>NACI does not recommend a universal program for vaccination of pregnant women given the current epidemiology in Canada</p> <p>In special circumstances, such as a regional outbreak situation, immunization with Tdap may be offered to pregnant women (≥ 26 weeks of gestation) irrespective of their immunization history.</p> <p>Every effort should be made to administer one dose of pertussis containing vaccine in adulthood. Therefore, one dose of combined diphtheria, tetanus, acellular pertussis containing vaccine (Tdap) can be offered to pregnant women (≥ 26 weeks of gestation) who have not been previously vaccinated against pertussis in adulthood.</p> |
| 4. Why | Pertussis continues to occur in a cyclic pattern every 2-5 years. The greatest morbidity and mortality occurs in children under 6 months of age. When an outbreak is occurring, vaccinating pregnant woman increases maternal antibody transfer. This provides immediate protection to infants who are at the greatest risk of morbidity and mortality, prior to the completion of their primary series. Vaccinating pregnant women also prevents them from acquiring infection that they may pass onto their newborn baby. |

I. INTRODUCTION

In 2012, a number of Canadian provinces and territories reported an increase in pertussis with a total of more than 4,800 cases reported nationally. This represents an approximate three-fold increase from the mean number of cases reported between 2005 and 2011.

The observed outbreaks in Canada as well as the recently adopted recommendations for immunization of pregnant women in other countries have prompted a review of existing advice to immunize pregnant women as a means of protecting infants prior to completion of their primary immunization series. In 2011, US Center for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) recommended that an acellular pertussis vaccine be administered to all pregnant women after 20 weeks gestation and in 2012 expanded this to recommend revaccination with every pregnancy between 27 and 36 weeks gestation.⁽¹⁾⁽²⁾ In 2012, UK's Department of Health announced the introduction of a temporary immunization programme for all pregnant women between 28-38 weeks of pregnancy during one of the country's largest pertussis outbreaks in several decades, which was associated with significant infant mortality.⁽³⁾ Compared to postpartum vaccination, vaccination in pregnancy could potentially reduce annual infant pertussis incidence by 33% versus 20%, hospitalizations by 38% versus 19%, and deaths by 49% versus 16%.⁽⁴⁾

Since 1998, immunization with an acellular pertussis vaccine has been recommended at 2, 4, 6 months of age and at 12 to 23 months of age (generally given at 18 months of age); in cases where rapid protection is required, the first dose can be given at 6 weeks of age. DTaP-IPV or Tdap-IPV should be used as the booster dose for children 4-6 years of age. Also, a booster dose of Tdap vaccine should be administered at 14-16 years of age. The National Advisory Committee on Immunization (NACI) recommends that all adults receive one dose of Tdap vaccine if not previously immunized in adulthood (18 years of age and older), with particular attention given to those who anticipate having regular contact with infants. Several Canadian jurisdictions including British Columbia,⁽⁵⁾⁽⁶⁾ the Yukon⁽⁷⁾ and New Brunswick⁽⁸⁾ have issued temporary provincial advisories recommending pregnant women be immunized in the last trimester of pregnancy or prior to discharge from hospital after delivery. Saskatchewan⁽⁹⁾ has also recommended that in certain high risk circumstances (such as outbreaks) pregnant women can be offered Tdap any time after 20 weeks gestation if they have not received an adult dose of Tdap.

At the NACI meeting in October 2012, NACI requested the Pertussis Working Group to review the evidence related to vaccination in pregnancy and consider the following questions:

- Review the epidemiology of pertussis in Canada
- Are pertussis vaccines safe for pregnant woman and their fetus if given during pregnancy?
- Do pertussis vaccines provide effective protection to pregnant women if given during pregnancy?
- Does vaccinating mothers increase the protection of infants?
- Does maternal antibody transferred across the placenta interfere with neonatal immune response to immunization?

NACI did not consider other public health strategies for preventing infant disease, such as vaccinating those in contact with infants (cocooning), due to the significant programmatic issues associated with its implementation.⁽⁴⁾⁽¹⁰⁾⁻⁽¹⁴⁾

II. METHODS

The Pertussis Working Group reviewed the key questions for the literature review as proposed by NACI, including such considerations as the burden of disease to be prevented and any evidence of change in the burden amongst different populations; safety, immunogenicity, efficacy, and effectiveness of the vaccines; vaccine schedules; and other aspects of the overall immunization strategy. Building on the work conducted by US CDC⁽¹⁾⁽¹⁵⁾ and UK Joint Committee on Vaccination and Immunisation (JCVI)⁽³⁾ a further literature search and review of articles published between January 1, 2011 to February 15, 2013 was completed. A total of 44 articles were identified, retrieved and included in the literature review to inform this statement. The knowledge synthesis was performed by two medical advisors at the Agency, and supervised by the Working Group. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Table 1 to 4) were prepared, and proposed recommendations for vaccine use developed. The Working Group Chair and PHAC medical advisors presented the evidence and proposed recommendations to NACI on May 15, 2013. Following thorough review of the evidence and consultation at the NACI meeting of June 6, 2013, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text below.

III. EPIDEMIOLOGY

For information on symptoms and natural progression of disease please refer to the Canadian Immunization Guide (CIG).⁽¹⁶⁾ (<http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pert-coqu-eng.php>)

Pertussis is an endemic and cyclical disease, which peaks at two to five year intervals. Pertussis cycles are asynchronous in Canada, with the timing of cyclic peaks in activity varying by province and territory. Despite periodic increases in disease activity, Canada has experienced an overall decline in the incidence of pertussis since 1998, from a high of 29.5 cases per 100,000 population to a low of 2.0 cases per 100,000 population in 2011. However, the severity of illness and complications following infection remain greatest among infants too young to be protected by a complete vaccine series. Average incidence rates from 2005 to 2011 were highest among infants less than 1 year of age at 72.2 cases per 100,000 population, followed by 1 to 4 year olds (25.6 cases per 100,000), and 10 to 14 year olds (16 cases per 100,000). For further details on the overall epidemiology of pertussis in Canada, please see the pertussis chapter of the Canadian Immunization Guide webpage (<http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pert-coqu-eng.php>) or PHAC's Vaccine Preventable Diseases (VPD) web page. (<http://www.phac-aspc.gc.ca/im/vpd-mev/>)

Based on preliminary data, in 2012, increased incidence rates relative to the annual average from 2005-2011 occurred in 8 provinces and territories with the largest increases being observed in New Brunswick and the Yukon. Other provinces with notable increases in pertussis infection included British Columbia, Manitoba, and Quebec. Among the 5 provinces/territories which experienced decreases in pertussis activity in 2012 relative to the annual average from 2005-2011, many had experienced peaks in activity in 2010 and/or 2011. In 2012, due to the increase in incidence across multiple jurisdictions, the national incidence of disease increased by almost 7-fold from what was reported in 2011 to 13.9 cases per 100,000 (n=4,845). The increase in incidence was observed across all age groups (range of 1.7 to 5.6 times greater relative to the mean 2005-2011) with the highest incidence rates in those less than one (120.8

per 100,000; n=460) and those 10-14 years of age (64.1 per 100,000; n=1203). As well in 2012, preliminary data show a total of 104 pertussis related hospitalizations that were reported through the Immunization Monitoring Program Active (IMPACT), an almost 2-fold increase from the number of hospitalizations in 2011 (n=55) and a 64% increase from the average annual number of hospitalization reported between 2005-2011 (n=63.5). Three deaths were reported in 2012, all in previously well infants without underlying medical conditions, who were less than two months of age. The number of reported deaths is in keeping with historical trends.

In general, adolescents and adults who have not been optimally protected through recommended immunization are at risk of infection and are at risk for passing the infection onto infants. Parents are an important source of pertussis transmission to young infants.⁽¹⁷⁾⁻⁽²⁴⁾ Specifically, the lack of maternal immunity increases susceptibility to pertussis infection in very young infants both by increasing the risk of infection in mothers and subsequent transmission to the infant, as well as by not providing the infant with sufficient passive protection transplacentally in the third trimester or through breast milk. Before completing the primary series of pertussis immunization, which is the period of highest risk for pertussis complications, infants rely on maternally transferred antibodies for protection. In Canada in 2011, the mean age of mothers at birth was 29.7 years and there were approximately 380 000 live births.⁽²⁵⁾⁽²⁶⁾

IV. VACCINE

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

| Brand name | Adacel® | Boostrix® |
|--|--|--|
| Immunogens | Tdap | Tdap |
| Manufacturer | Sanofi | GSK |
| Authorization | - booster dose 4 years of age and above | - booster dose 4 years of age and above - not intended for primary immunization |
| Antigen Components (µg) | | |
| Pertussis Toxoid (PT) | 2.5 | 8 |
| Pertussis filamentous hemagglutinin (FHA) | 5 | 8 |
| Pertussis pertactin (PRN) | 3 | 2.5 |
| Pertussis fimbriae (FIM 2/3) | 5 | - |
| Diphtheria Antigen (Lf) | 2 | 2.5 |
| Tetanus Antigen (Lf) | 5 | 5 |
| Other ingredients | Aluminum phosphate, 2-phenoxy-ethanol, water | Aluminum phosphate, Aluminum hydroxide, water, glycine, sodium chloride and polysorbate 80 |

| Brand name | Adacel® | Boostrix® |
|---------------|------------------------------|------------------------------|
| Trace Amounts | formaldehyde, glutaraldehyde | formaldehyde, glutaraldehyde |

*IPV containing vaccine preparations also exist (eg Adacel-Polio, Boostrix-Polio). IPV vaccine may be considered for pregnant women who require immediate protection and are at increased risk of exposure to wild poliovirus. There is no evidence to suggest a risk to the fetus or to the pregnancy from maternal immunization with inactivated vaccines, such as IPV vaccine.⁽¹⁶⁾

IV.2 Effectiveness and duration of protection

The vaccine efficacy following the primary series with acellular pertussis vaccines is estimated to be about 85%, and approximately 90% following booster immunization.⁽²⁷⁾⁽²⁸⁾⁻⁽³⁰⁾ However, the true vaccine effectiveness of acellular pertussis vaccines is difficult to determine because few surveillance systems have the capacity or data quality to calculate this accurately (including Canada). In addition, the clinical trials case definition provided by the World Health Organization (WHO) does not account for milder cases, and may artificially inflate efficacy.⁽³¹⁾

Although the duration of protection remains unknown, available data suggests that protection does not significantly decline in the first four years following the primary and booster immunization with an acellular pertussis vaccine.⁽²⁸⁾⁻⁽³⁰⁾ Two recent studies indicate waning of immunity over the five years after the fifth dose of DTaP. In the Klein et al study (2012), after the fifth dose of DTaP, the odds of acquiring pertussis increased by an average of 42% per year in those vaccinated over 5 years before.⁽³²⁾ Misegades et al (2012) also investigated the vaccine effectiveness (VE) in children after receipt of five doses of pertussis containing vaccine.⁽³³⁾ Using a case-control design, they showed that VE declined each year after the fifth dose of DTaP. Their estimates of VE based on time since the fifth dose were as follows: 98.1% (95% CI 96.1-99.1) for those within one year of receipt; 95.3% (95% CI 91.2-97.5) for those 12-23 months since last dose; 92.3% (95% CI 86.6-95.5%) for those 24-35 months since last dose; 87.3% (95% CI 76.2-93.2) for those 36-47 months since last dose; 82.8% (95% CI 68.7-90.6) for those 48-59 months since last dose; and 71.2% (95% CI 45.8-84.8) in those greater than 60 months since last dose of DTaP.

Effectiveness and duration of maternal and infant protection following vaccination in pregnancy has not been studied.

IV.3 Immunogenicity

Immunologic correlates of protection against pertussis are not well defined, but higher levels of antibodies (pertussis toxin (PT); pertactin (PRN); fimbriae (FIM)) seem to be associated with greater protection.⁽³⁴⁾⁻⁽³⁷⁾ In previously immunized adults, booster vaccination produces antibody responses to pertussis after 7 days and peak antibody levels are reached 10–14 days after vaccination.⁽³⁸⁾⁽³⁹⁾ Following vaccination with acellular pertussis vaccines, antibody levels rapidly decrease in the first year and approach pre-vaccination levels by end of third year.⁽⁴⁰⁾⁽⁴¹⁾

Although pregnancy is considered to be an immunomodulatory condition, conducted serological studies indicate that the immune response following vaccination with Tdap is comparable between pregnant and non-pregnant women.⁽⁴²⁾ Studies measuring the levels of anti-pertussis

antibody in maternal sera after immunization have demonstrated similar trends to those seen in non-pregnant women following vaccination.⁽¹⁰⁾⁽³⁸⁾⁽⁴¹⁾⁽⁴³⁾⁽⁴⁴⁾

Administration of Tdap immediately before or during pregnancy has demonstrated significantly higher concentrations of antibodies in the cord blood of newborn infants as compared to infants whose mothers were not vaccinated in this time period.⁽³⁴⁾⁽⁴²⁾⁽⁴³⁾⁽⁴⁵⁾⁻⁽⁴⁸⁾ Several studies provide evidence of effective maternal antibody transfer via the placenta to the newborn with the degree of transfer appearing to be dependent on the amount of maternal antibody in circulation.⁽³⁴⁾⁽⁴³⁾⁽⁴⁶⁾ Passive transfer of maternal antibodies begins after 28 weeks of gestation and is followed by active/preferential antibody transfer after 32-33 weeks of gestation leading to higher antibody levels in infants than in mothers at birth.⁽⁴⁴⁾ Following birth, the level of pertussis antibodies declines in the newborn. The half-life of transferred maternal pertussis antibodies has been estimated to be between 5 and 6 weeks and the majority of infants will not have any detectable maternal pertussis antibodies by the age of 2 to 6 months.⁽⁴⁴⁾⁽⁴⁷⁾

Does transplacental transfer of pertussis antibody from mother to child interfere with the infant immune response to the active pertussis immunization primary series?

Van Savage et al investigated a small group of infants (n=23) who had either 'high' or 'low' levels of transplacental antibodies – both groups were able to mount similar antibody responses to their primary series acellular pertussis vaccine.⁽⁴⁷⁾ Englund et al found that there was no adverse relationship with the PT antibody level measured pre immunization and an infants' post immunization antibody level after three doses of pertussis containing vaccine. However, higher pre immunization levels of FHA, PRN, FIM antibodies did show a statistically significant negative effect on the level of antibody measured in infants one month after a three-dose schedule (i.e. at 2,4, and 6 months).⁽⁴⁹⁾ Hardy-Fairbanks et al compared the immune responses of 16 infants whose mothers received Tdap during pregnancy to controls and found that they had substantially higher pertussis antibodies from birth through the first few months of life, slightly lower levels at 7 months (after third DTaP), but similar levels before and after the booster dose of DTaP at 12–18 months.⁽⁵⁰⁾ A randomized controlled trial of 48 mother/infants pairs by Munoz et al⁽⁴²⁾ showed there was no difference in antibody levels after the primary series and following the first booster dose at 12 months in infants of mothers vaccinated compared to infants whose mothers did not receive Tdap in pregnancy.

Preliminary, blinded results from an ongoing trial by Halperin et al⁽⁵¹⁾ have suggested an increased level of antibodies in one group at 2 months of age prior to receiving the first dose of the primary series. Interim immunogenicity analysis of 50 infants demonstrated significant differences in antibody levels at 7 months of age, particularly for the FIM antibody. In the group that had had an increased level of antibody at 2 months of age, there was a decreased level of antibodies at 7 months of age suggesting possible interference in the immune response. This study expects to complete enrolment in December 2013. In comparing the data reported by Munoz et al⁽⁴²⁾⁽⁵²⁾ and Halperin et al,⁽⁵¹⁾ the absolute values of antibody levels measured between the two studies were quite similar. It is possible that the Munoz et al⁽⁴²⁾⁽⁵²⁾ study was underpowered to detect a difference in antibody levels. Further information will be available from the Halperin et al⁽⁵¹⁾ study after completion and unblinding of the treatment versus control group.

In general, immunization following 26 weeks' of gestation has been shown to be immunogenic and maximizes the transfer of maternal antibodies to the fetus. However, there is limited evidence regarding the effect of maternal antibodies on the infant immune response to routine infant DTaP vaccination and the potential for increased risk of pertussis later in life.

IV.4 Adverse Events

In non-pregnant healthy adolescents and adults Tdap is a safe and well tolerated vaccine with some injection-site reactogenicity. Most common adverse events following vaccination include pain, redness, swelling and headache. Receipt of a second dose of Tdap at a 5- or 10-year interval in healthy non-pregnant adolescents and adults does not seem to increase the frequency or intensity of adverse events;⁽⁵³⁾⁻⁽⁵⁶⁾ Safety data on use of Tdap during multiple pregnancies have not been published, but may be available in the coming years following the ACIP recommendation to administer Tdap during every pregnancy. For a more detailed discussion on adverse events related to Tdap, please see the CIG.⁽⁵³⁾⁻⁽⁵⁵⁾⁽⁵⁷⁾⁽¹⁶⁾

Data on the safety of administering Tdap to pregnant women and the fetus are available through several small studies, the US Vaccine Adverse Event Reporting System (VAERS), the UK Clinical Practice Research Datalink (CPRD), and published and unpublished data from Sanofi Pasteur's (Adacel®) and GlaxoSmithKline's (Boostrix®) registries.

Correct interpretation of adverse events following vaccination in pregnancy using registry data requires adequate knowledge of background or expected rates of complications that are not related to immunization.⁽⁵⁸⁾ In a population of pregnant women it is expected that there would be 12 to 14.5 spontaneous abortions per 100 pregnancies,⁽⁵⁸⁾ 10.4 – 11.5% of babies would be born prematurely and 1-3% of babies would be born with congenital anomalies.⁽⁵⁹⁾

In a self-reported survey following a mass immunization program of health care workers in a tertiary hospital with a pertussis outbreak, Talbot et al (2010)⁽⁶⁰⁾ reported that out of 16 women pregnant at the time of vaccination only one reported severe swelling at the injection site and two reported fever (not documented) in the 2 weeks after Tdap. None of the respondents reported serious adverse events. All 16 women reported delivering healthy term newborns. Similarly, in a trial conducted by Gall et al (2011)⁽⁴⁸⁾ there were no adverse reactions to pertussis vaccine administration reported by the 52 women participating in the trial.⁽⁴⁸⁾ This study did not specifically report on infant related safety outcomes. A post-marketing safety evaluation study was reported by Klein et al (2010)⁽⁶¹⁾; in their cohort of 6550 female adolescents from 10-18 years of age, three pregnancies were reported in Tdap recipients.⁽⁶¹⁾ One reported pregnancy ended in miscarriage at 8 weeks gestation and was not considered to be related to vaccination, while the other 2 pregnancies resulted in normal healthy offspring. In a randomized control trial (RCT) conducted by Munoz et al,⁽⁴²⁾ 33 women received Tdap during the 3rd trimester and 15 women received placebo. There were no significant differences in adverse events reported and all pregnant women delivered healthy infants, 92% at term. In another RCT, an interim blinded safety analysis of 50 women by Halperin et al⁽⁵¹⁾ showed similar results with no significant adverse events reported in either of the groups.

Zheteyeva et al (2012)⁽⁶²⁾ conducted a search of VAERS from January 2005 through June 2010. This surveillance system provides passive data on adverse events that are reported following vaccination. The study identified 132 reports of Tdap administered to pregnant women. Of the reports, 55 (42%) reported on vaccine administered to a pregnant woman with no adverse events having occurred. Spontaneous abortion was reported in 22 (16.7%) with injection site reaction being reported by 6 (4.5%). There were six adverse events reported in infants with only one serious adverse event (gastroschisis). The authors concluded that there was no safety signal identified in pregnant women or infants when pertussis vaccine was given in pregnancy. The CDC is also planning on reviewing the Vaccine Safety Data link (VSD) for adverse events related to immunizing pregnant women with Tdap. The VSD includes a large linked database that uses administrative data sources at nine managed care organizations which gather data on

vaccination (vaccine type, date of vaccination, concurrent vaccinations), medical outcomes (outpatient visits, inpatient visits, urgent care visits), birth data, and census data. It is anticipated these data will not be available for approximately 5 years from introduction of their maternal pertussis immunization program in 2010.

Following the implementation of the UK outbreak-related maternal pertussis immunization program, an analysis of the Clinical Practice Research Datalink (CPRD) data was conducted. A total of 12 000 vaccinated women with at least 2 weeks post vaccination follow up data was analysed. This research database, using vaccination and clinical data, did not detect an increased immediate or later pregnancy risk of any of the pre-specified events (intrauterine death, stillbirth, pre-eclampsia, eclampsia, ante-/ post-partum haemorrhage, uterine rupture, placenta praevia, vasa praevia, fetal distress and pre-term birth).⁽⁶³⁾

The Sanofi Pasteur Adacel® pregnancy registry has previously been used to review clinical trial or spontaneously reported adverse events following Tdap vaccination in pregnancy.⁽⁶⁴⁾⁽⁶⁵⁾ The most recent review of registry data conducted in October 2012 analyzed a total of 1083 reported cases with Tdap exposure in women within 30 days before last menstrual cycle or during pregnancy. Out of these, 270 were reported in clinical trials/phase IV studies, 1 case was retrieved in the literature and 812 were spontaneously reported to the manufacturer. Review of spontaneous abortion cases did not indicate any safety concern. In the few cases of the reported congenital anomalies, no pattern of anomaly was observed and the role of the vaccine was considered unlikely. Overall, available data through the registry does not suggest increased concern for maternal or infant health after receipt of Adacel®.

The GlaxoSmithKline (GSK) product Boostrix® related information is collected through the Worldwide Safety database and the GSK Pregnancy Registry. The number of pregnancies and outcomes reported was deemed by GSK to be insufficient for reaching reliable and definitive conclusions about the safety of vaccination with Boostrix® during pregnancy.

Overall, the current data suggests a good safety profile of Tdap vaccination in pregnancy, although it is not sufficient to exclude occurrence of rare adverse events in mother or newborn. However, this potential risk appears to be unlikely. Tetanus and combined tetanus and diphtheria vaccines have a well-established safety record when given during pregnancy. They have not been shown to adversely affect mothers or their infants.⁽⁶⁶⁾⁻⁽⁶⁹⁾

V. RECOMMENDATIONS

Recommendation #1

In view of the current pertussis epidemiology in Canada NACI does not recommend universal immunization of all women against pertussis during pregnancy (NACI Recommendation Grade E)

There is significant variation among provinces and territories in pertussis epidemiology with jurisdictions experiencing increases in pertussis activity at different times and at different levels. To date, the vaccine has been shown to be safe and immunogenic in pregnant women, the effectiveness to prevent severe disease in newborns is not established, and the potential to interfere with the infant's immune response is not yet defined. The epidemiology of pertussis in Canada will continue to be monitored closely as will the experiences of other jurisdictions who have implemented maternal immunization policies in response to increased disease activity.

Recommendation #2

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 gestation or greater irrespective of their immunization history. (NACI Recommendation Grade B)

Pertussis protection following immunization wanes with time. Immunization with Tdap to date has been shown to be safe in pregnant women and allows higher levels of antibody to be transferred to newborns during the first two months of life when the morbidity and mortality from pertussis infection is the highest. Immunization may be offered at any prenatal appointment after 26 weeks gestation (e.g. a convenient time may be the 28 week visit when pregnant women are routinely seen for glucose tolerance testing). Immunization should not be delayed until close to delivery since this may provide insufficient time for optimal transfer of antibodies and direct protection of the infant against pertussis.

Recommendation #3

Independent of regional epidemiology, pregnancy is an opportunity to review immunization status with mothers and offer a pertussis vaccine at that time if it has not already been received in adulthood. (NACI Recommendation Grade A)

Every opportunity should be used to maximize immunization coverage in adulthood, particularly for adults who have contact with infants and young children. As currently recommended by NACI, adults should receive at least one dose of pertussis containing vaccine in adulthood. All pregnant women following 26 weeks of pregnancy who have not received a dose of a pertussis containing vaccine in adulthood should be encouraged to receive Tdap vaccination. For further information on routine adult immunizations please refer to CIG.

Recommendation #4

Jurisdictions should have the capacity to continuously monitor and rapidly respond to changes in pertussis epidemiology and actively encourage vaccine providers to immunize pregnant women in case of increased pertussis incidence, hospitalizations or deaths. (NACI Recommendation Grade A)

Recommendation #5

To complement implementation and allow evaluation of an immunization program for pregnant women, NACI recommends jurisdictions that offer pertussis immunization in pregnancy also establish mechanisms to monitor vaccine coverage and safety. (NACI Recommendation Grade A)

Given the limited data available on pertussis vaccine in pregnancy, evaluating such a program will be essential as the epidemiology of pertussis changes. Safety monitoring will provide additional reassurance to providers as well as the public. Mechanisms to conduct such monitoring should be implemented in conjunction with implementation of the program. Some programs (ie CAEFISS) are already in place for safety monitoring, but additional complementary/enhanced maternal surveillance (i.e. through immunization registries) or special studies will also need to be conducted.

VI. RESEARCH PRIORITIES

Research to address the following outstanding questions related to immunization in pregnancy is encouraged:

- further work on determining the impact of maternal vaccination on an infant's immune response
- further work on determining the optimal timing of maternal vaccination
- vaccine effectiveness and immunogenicity studies for pertussis in women and their newborns when the women have been immunized in pregnancy
- knowledge and attitudes of physicians and parents related to immunization in pregnancy
- implementation and programmatic research related to the optimal process for delivering immunizations to pregnant women
- qualitative studies to understand a physicians'/patients' decision making around whether to offer/accept pertussis vaccine while pregnant

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 and the duration of protection provided by acellular pertussis vaccine in adolescence and adulthood
- determining the optimal schedule for Tdap vaccination in adolescence and adulthood
- vaccine effectiveness studies for pertussis in adolescents and adults
- optimal outbreak prevention and control strategies/activities during periods of low/high disease activity
- improving the diagnosis of pertussis at the primary health care level

VII. SURVEILLANCE 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
- surveillance on mother-infant dyads that have received vaccine
- 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
- investigate the use of a case definition which allows for milder cases of pertussis⁽⁷⁰⁾
- active safety evaluation and surveillance including use of linked administrative data
- improving methods of assessing vaccine coverage (comprehensive immunization registries)
- improving collaboration between public health and industry in Canada and internationally on monitoring disease activity, vaccine safety and program outcomes
- use of surveillance data as part of program evaluation

TABLES

Table 1. Summary of evidence related to immunogenicity of acellular pertussis vaccination in pregnancy (mother)

| STUDY DETAILS | | | | | SUMMARY |
|-------------------------------------|--|--|--|---|-------------------------------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings Using Text or Data | Level and Quality of Evidence |
| Healy CM et al 2013 ⁽⁴⁴⁾ | Tdap | Serological study -Convenience sample | N=105 women who received a Tdap vaccine 2 to 24 months before delivery N=19 women who received Tdap during pregnancy (16 of 19 immunized before week 20 of gestation) | IgG concentrations at the time of delivery: PT 10.5(6.4-17.1) FHA 49.3 (28.4-85.8) FIM 103.1 (42.7-249) PRN 40.4 (18.9-87.3) | II-3, good |
| Healy et al. 2004 ⁽⁴³⁾ | Routine US vaccine schedule | Serological study Convenience sample | N= 64 pregnant women | GMC (95%CI) maternal PT 2.4 (1.9-3.1) FHA 6.9(5-9.5) FIM 13.0 (9.2-18.5) | II-3, good |
| Gall et al. 2011 ⁽⁴⁸⁾ | Tdap (Sanofi Pasteur – (prenatal or 2 nd trimester) | Cohort (vaccine offered, chart review, blood collected and stored) | Pregnant women Oct 2008 to Dec 2009 N= 104 pairs 52 rec'd antenatal vaccine 52 no vaccine | Indirect measure of immunogenicity (maternal serum concentrations not reported): Newborn antibody level – mean (SEM)– moms without vaccine vs moms with vaccine PT 11 (1.8) vs 28.2 (2.8) (p<0.001) FHA 26.8 (4.0) vs 104.1 (21.7) (p=0.002) PRN 24.7 (5.8) vs 333.0 (56.4) (p<0.001) FIM 82.8 (14.6) vs 1199.0 (189.9) (p<0.001) | II-2, good |

Table 2. Summary of evidence related to immunogenicity of acellular pertussis vaccination in pregnancy (baby)

| Evidence related to passive immunity following acellular pertussis vaccination before and during pregnancy | | | | | |
|--|----------------------------------|--|--|--|-------------------------------|
| STUDY DETAILS | | | | | SUMMARY |
| Study | Vaccine | Study Design | Participants | Summary of Key Findings Using Text or Data | Level and Quality of Evidence |
| Leuridan, E et al. 2011 ⁽⁴⁵⁾ | Tdap (Boostrix®) | Prospective Cohort Vaccine offered between pregnancy one and two | Non pregnant women between pregnancies N=86 but interim analysis n=24 | GMT (95%CI) maternal vs cord vs 1 mos infant PT 12.1(7.3-19.9) vs 19.0 (11.7-30.7) vs 10.3 (6.3-16.8) FHA 133.2 (89-199.4) vs 247 (161-379) vs 152.1(104-220) PRN 160.4 (94.6-271.8) vs 278 (154-502) vs 167.4 (102-274) | II-2, good |
| De Voer et al. 2009 ⁽³⁴⁾ | Dutch routine childhood schedule | Retrospective, cohort analysis -blood was stored from 2004-2006 study | N=197 maternal and cord blood pairs | GMC (95%CI) maternal vs cord PT 9.9 (8.6-11.3) vs 16.2 (14.2-18.3) FHA 21.5 (18.6-24.8) vs 34.8 (30.1-40.1) PRN 13.5 (11.7-15.6) vs 17.7 (15.2- 20.5) -therefore good transfer of transplacental Ab from mom to babe Maternal ab were at low [] PT (20%), FHA (48%) PRN (32%) | II-3, good |
| Healy et al. 2004 ⁽⁴³⁾ | Routine US vaccine schedule | -blood stored from 1999-2000 | N= 64 | GMC (95%CI) maternal vs cord vs infant (2 months of age) PT 2.4 (1.9-3.1) vs 4.1(3-5.5) vs 1.4(1.2-1.7) FHA 6.9(5-9.5) vs 12.3 (8.8-17.3) vs 3.0 (2.3-3.8) FIM 13.0 (9.2-18.5) vs 20.4 (14-29.6) vs 5.8 (4.5-7.4) | II-3, good |

| STUDY DETAILS | | | | | SUMMARY |
|--|--|--|--|--|-------------------------------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings Using Text or Data | Level and Quality of Evidence |
| Shakib et al. 2010 ⁽⁴⁶⁾ | Routine childhood immunization (none given as a part of study) | Observational study | N=81 mother-infant pairs | <p>-numeric GMT not given</p> <p>-% with above PT (>5 EU) and FIM and PRN >10EU, mom vs baby 21% vs 26%</p> <p>7 mothers had titres suggestive of recent pertussis infection (past 7-10 yrs)</p> <p>Comparing infants whose moms had recent pertussis and those who didn't:</p> <p>Mean FIM - 145 vs 32.9 Mean PRN - 43.4 vs 16.7 Mean PT - 21.4 vs 9.4</p> <p>At 6 weeks: infant -% with above PT (>5 EU) and FIM and PRN >10EU 43% vs 8%</p> | III, fair |
| Van Savage et al. 1990 ⁽⁴⁷⁾ | 1) Routine US schedule, 2) Whole cell or acellular vaccine 3) no vaccine | Group 1: convenience sample Group 2: RCT Group 3: longitudinal study | N=34 maternal +cord serum N=50 infants (after 3 doses whole cell or acellular vaccine) N=17 no vaccine | <p>GMT (95%CI) maternal vs cord</p> <p>Group 1 LPF 4.9 (1.8-13.4) vs 14.0 (6.1-32.1) FHA 41.4 (26.1-65.6) vs 26.8 (14.5-49.4) Agglutinins 34.0 (23.3-49.7) 34.7 (23.5-51.3)</p> <p>Group 2: Tdap – no decrease in antibody response based on high or low levels of transplacental antibodies.</p> <p>Group 3: t_{1/2} to LPF 36.3 days, FHA 40.3 days, agglutinins 55 days</p> | III, fair |

| STUDY DETAILS | | | | | SUMMARY |
|-------------------------------------|---|--------------|----------------|---|-------------------------------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings Using Text or Data | Level and Quality of Evidence |
| Englund et al. 1995 ⁽⁴⁹⁾ | DTaP or DwTP in use in US (total of 15 different formulations) Given at 2, 4, 6 mos of age | RCT | N=2342 infants | At 7 mos of age (after 3 doses of pertussis containing vaccine): -PT antibody levels did not lead to an improvement in response or decrease in response when compared to maternal antibody level -there was a statistically significant negative effect on FHA, PRN, FIM, AGG and DIP levels (ie if mom had high level of antibody then baby had lower level of ab after age appropriate immunization (linear regression model) | I, fair |

Evidence related to active immunity following acellular pertussis vaccination in pregnancy

| STUDY DETAILS | | | | | SUMMARY |
|----------------------------------|--|----------------------|--|--|-------------------------------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings Using Text or Data | Level and Quality of Evidence |
| Gall et al. 2011 ⁽⁴⁸⁾ | Tdap (Sanofi Pasteur – (prenatal or 2 nd trimester) | Retrospective Cohort | Pregnant women Oct 2008 to Dec 2009 N= 104 pairs 52 rec'd antenatal vaccine 52 no vaccine | Newborn antibody level – mean (SEM)– moms without vaccine vs moms with vaccine PT 11 (1.8) vs 28.2 (2.8) (p<0.001) FHA 26.8 (4.0) vs 104.1 (21.7) (p=0.002) PRN 24.7 (5.8) vs 333.0 (56.4) (p<0.001) FIM 82.8 (14.6) vs 1199.0 (189.9) (p<0.001) | II-2, good |

Table 3. Summary of evidence related to safety of acellular pertussis vaccine in pregnancy (mother)

| Evidence related to safety of acellular pertussis vaccine in pregnancy (mother) | | | | | |
|---|--|---|--|---|-------------------------------|
| STUDY DETAILS | | | | | SUMMARY |
| Study | Vaccine | Study Design | Participants | Summary of Key Findings Using Text or Data | Level and Quality of Evidence |
| Gall et al. 2011 ⁽⁴⁸⁾ | Tdap (Sanofi Pasteur – (prenatal or 2 nd trimester) | Retrospective Cohort | Pregnant women Oct 2008 to Dec 2009 N= 52 | There were no adverse reactions to the vaccine. | II-2, good |
| Munoz et al. 2013 ⁽⁴²⁾ | Tdap | Randomized, double masked placebo control trial | N=48 18-45 year old pregnant women: Tdap (33) vs saline (15) | No significant differences in the frequency of injection-site reactions between groups. Fever occurred in 3% of pregnant women vs. 9.4% non-pregnant. | (n/a) abstract |
| Zheteyeva YA et al. 2012 ⁽⁶²⁾ | Boostrix® (GSK) Adacel® (Sanofi) | Passive Surveillance System Review-Vaccine Adverse Event Reporting System (VAERS) | Population based (women only) Jan 2005 to June 2010 | The most frequent non-pregnancy specific outcomes were injection site reactions in 6 (4.5%) reports, followed by anemia (5, 3.8%) and headache or fever with abdominal pain (3, 2.3%) | II-3, fair |
| Talbot et al. 2010 ⁽⁶⁰⁾ | Adacel® (Sanofi) | Observational Study | Sample of 4524 health care workers | Data collected through interview -16 pregnancies -1 reported severe swelling at the injection site and 2 reported feeling feverish (without documented fever) in the 2 weeks after Tdap; they recovered without treatment | III, fair |

Table 4. Summary of evidence related to safety of acellular pertussis vaccine in pregnancy (baby)

| Evidence related to safety of acellular pertussis vaccine in pregnancy (baby) | | | | | |
|---|--|--|------------------------------------|---|-------------------------------|
| STUDY DETAILS | | | | | SUMMARY |
| Study | Vaccine | Study Design | Participants | Summary of Key Findings Using Text or Data | Level and Quality of Evidence |
| Englund JA et al. 1995. ⁽⁴⁹⁾ | 13 different acellular vaccine formulations (vary from 1 to 4 pertussis antigens) 2 whole cell vaccine formulations | Randomized Controlled Trial Subset of NIAID Multicenter Acellular Pertussis Trial | N=2096 2 month old infants | -parental reaction diary 48 hours after vaccination -phone call to parents -fever, redness, swelling, fussiness and pain -serious adverse reactions -analysis based on a simple linear regression equation (independent variable log of preimmunization antibody level, dependent variables combination of 4 antibodies [PT, FHA, PRN, FIM] and reactions) -yielded 20 regression equations -only one statistically significant – swelling and preimmunization PT antibody (p=0.14) | I, fair |
| Talbot et al. 2010 ⁽⁶⁰⁾ | Adacel® (Sanofi) | Observational Study | Sample of 4524 health care workers | Data collected through interview -16 pregnancies -no adverse outcomes in babies | III, poor |
| Wang, M et al. 2011 ⁽⁶⁵⁾ | Adacel® (Sanofi) | Passive Surveillance – Drug manufacturer registry | Review from Jun 2005 to Jan 2011 | -480 spontaneous reports -27 (5.6%) serious adverse events -16 (3.3%) spontaneous abortions -8 (1.7%) preterm deliveries | n/a (abstract) |

| STUDY DETAILS | | | | | SUMMARY |
|--|-------------------------------------|---|--|--|-------------------------------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings Using Text or Data | Level and Quality of Evidence |
| Zheteyeva YA et al. 2012 ⁽⁶²⁾ | Boostrix® (GSK) Adacel® (Sanofi) | Passive Surveillance System Review-Vaccine Adverse Event Reporting System (VAERS) | Population based (women only) Jan 2005 to June 2010 | -6 adverse outcomes were reported in infants whose mother's received Tdap -included one of each of the following: gastroschisis, laryngomalacia, patent foramen ovale, mild physiologic jaundice, transient tachypnea, bilateral hydroceles | II-3, fair |
| Munoz et al. 2013 ⁽⁴²⁾ | Tdap | Randomized, double masked placebo control trial | N=48 18-45 year old pregnant women: Tdap (33) vs saline (15) | All pregnant women delivered healthy infants , 92% at term. There were no differences in the rates of C-section, infant birth weight, gestational age, Apgar score or hospital course. | n/a (abstract) |
| Klein NP, et al. 2010 ⁽⁶¹⁾ | Tdap (Boostrix®) | Open, prospective, observational study | N= 13,427 10 to 18-year-old adolescents | Three pregnancies reported in Tdap recipients: -One miscarriage at 8 weeks gestation. The miscarriage was not considered to be related to vaccination. -Other 2 pregnancies resulted in normal healthy offspring. | I, poor |

Table 5. Levels of Evidence Based on Research Design

| | |
|------|--|
| 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 6. Quality (internal validity) Rating of Evidence

| | |
|------|--|
| 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 7. NACI Recommendation for Immunization -- Grades

| | |
|---|--|
| A | NACI concludes that there is good evidence to recommend immunization. |
| B | NACI concludes that there is fair evidence to recommend immunization. |
| C | NACI concludes that the existing evidence is conflicting and does not allow making a recommendation for or against immunization; however other factors may influence decision-making. |
| D | NACI concludes that there is fair evidence to recommend against immunization. |
| E | NACI concludes that there is good evidence to recommend against immunization. |
| F | NACI concludes that there is insufficient evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making. |

LIST OF ABBREVIATIONS

| <i>Abbreviation</i> | <i>Term</i> |
|----------------------------|--|
| ACIP | Advisory Committee on Immunization Practices (US) |
| AGG | Agglutinins |
| 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 |
| CPRD | Clinical Practice Research Database (UK) |
| DIP | Diphtheria toxin/toxoid |
| DTaP | Diphtheria, tetanus and acellular pertussis vaccine |
| DTwP | Diphtheria, tetanus, whole cell pertussis vaccine |
| FHA | Pertussis filamentous hemagglutinin |
| FIM | Fimbriae |
| FIM 2/3 | Pertussis fimbriae |
| GMC | Geometric mean concentration |
| GMT | geometric mean titre |
| IMPACT | Immunization Monitoring Program Active |
| JCVI | Joint Committee on Vaccination and Immunization (UK) |
| Lf | Limit of flocculation |
| LPF | Lymphocyte proliferating factor |
| PRN | Pertactin |
| PT | Pertussis Toxin |
| RCT | Randomized Controlled Trial |
| Tdap | Tetanus, diphtheria and 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 |

ACKNOWLEDGMENTS

†**NACI Members:** Dr. B. Warshawsky (Chair), Dr. I. Gemmill (Vice-Chair), Dr. B. Henry, Dr. D. Kumar, Dr. C. Quach-Thanh, Dr. M. Salvadori, Dr. B. Seifert, Dr. N. Sicard, Dr. W. Vaudry, Dr. R. Warrington.

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†This statement was prepared by Dr. S. Desai, Dr. O. Baclic, Ms T. Smith and approved by NACI.

NACI gratefully acknowledges the contribution of: Dr. C. Baker, Dr. E. Castillo, Dr. T. Clark, Dr. K. Donegan, Dr. A. Doroshenko, Dr. S. Halperin and Dr. P. McIntyre.

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