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Pertussis immunization in pregnancy in Ontario: scientific and technical considerations

Technical Report

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Public Health Ontario

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Contents

Overview and objectives

The purpose of this report is to describe and summarize the key scientific and technical information that is needed to inform decision making in Ontario in response to the National Advisory Committee on Immunization (NACI) 2018 recommendation that: Maternal immunization with tetanus, diphtheria and acellular pertussis (Tdap) vaccine should ideally be provided between 27 and 32 weeks of gestation. NACI further advised that Tdap immunization may be provided from 13 weeks up to the time of delivery in view of programmatic and unique patient considerations.

This report comprises a short summary of the NACI statement, a discussion of the evidence related to burden of infant pertussis in Ontario, and a description of potential policy and implementation considerations in the Ontario context with reference to components of the Erickson and De Wals framework[1] that are not covered by NACI's mandate.

Important context for this report is to reiterate the goal of pertussis immunization in pregnancy, which is primarily to protect infants from severe disease and death.[2] This is because pertussis immunization is most effective at preventing severe disease, which almost exclusively affects infants and young children. Pertussis vaccination is less effective at preventing mild infections, which predominanty occur in older children and adults. Protection also wanes over time, partly explaining mild cases in older children.

Summary of NACI considerations for pertussis vaccination in pregnancy

Vaccine effectiveness

Several countries have introduced programs for pertussis vaccination during pregnancy, providing a growing body of evidence that vaccination during pregnancy is highly effective at preventing infant pertussis.

The United Kingdom (UK) introduced a maternal pertussis vaccine program in 2012, initially at 28-32 weeks in every pregnancy, and since April 2016 from 16-32 weeks of pregnancy (usually at the fetal anomaly scan at 18-20 weeks).[3] The UK has conducted an intensive program evaluation that provides strong evidence for the effectiveness of maternal vaccination in preventing pertussis in newborn infants. Recent publications from the UK suggest that estimates of VE for protecting infants range from 82-95%.[4,5] Dabrera et al. (2015) conducted an unmatched case-control study which found vaccine effectiveness (VE) of maternal immunization between 28 and 38 weeks of gestation to be 93% (95% confidence interval (CI): 81 to 97%) in newborns, prior to the child receiving their own diphtheria, tetanus and acellular pertussis (DTaP) vaccination after adjusting for sex, geographical area and time of year of birth.[4] Amirthalingam et al. (2014) estimated that vaccination of mother in weeks 28-32 of pregnancy resulted in VE of 90% (95%CI: 86 to 93%) against pertussis for infants who were less than 2 months old, and 91% (95% CI: 88-94%) in infants less than 3 months old, in the year following the implementation of the UK program.[5] Vaccine effectiveness against infant pertussis-related death was estimated at 95% (95% CI: 79-100%) in a follow-up study.[6]

In the United States (US), the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) in 2011 began recommending that pregnant women be immunized with Tdap. Initially immunization was recommended for women not previously vaccinated with Tdap, and in February 2013, ACIP extended this to all pregnancies.[7] The recommendation is for immunization during the third trimester, optimally at between 27 to 36 weeks gestation.[7] A retrospective cohort study of infants in northern California estimated VE of maternal pertussis vaccination for protecting newborns from disease at 91.4% (95%CI: 19.5 to 99.1%) during the first two months of life and 69.0% (95%CI: 43.6-82.9%) during the first year of life.[8] There is also evidence that prenatal pertussis vaccination of mothers can reduce the severity of disease in infants. Winter et al. (2017) reports a VE of maternal vaccination in preventing hospitalization in infants with pertussis at 58% (95% CI: 15 to 80%) after adjusting for chronological and gestational age and infant receipt of pertussis vaccine.[9]

Overall, pertussis vaccination in pregnancy appears to be highly effective at preventing and reducing the severity of infant disease.

Impact of maternal immunization in pregnancy on the infant's response to immunization

The data are clear that immunization during pregnancy has an impact on the infant's response to their infant immunizations, with lower antibody levels achieved after the first doses of vaccines ("immune blunting").[10] Data also indicate that this immune blunting extends into the second year of life.[11]However, since there is no correlate of protection for pertussis, the significance of this immune blunting is unclear. Uncertainty about whether or not this was important was one of the reasosn that in an earlier statement, NACI did not recommend universal pertussis immunization in pregnancy. However, that position changed with the emergence of additional evidence of benefit to offset this theoretical concern. Furthermore, early data from the UK shows no increased risk of disease in children of immunized mothers, although this issue requires careful and long term monitoring as part of the routine overall evaluation that is conducted through surveillance of pertussis immunization programs.[6]

Vaccine Safety

The safety of Tdap vaccine in pregnancy is supported indirectly through a long history of tetanus vaccination in pregnancy in efforts to eliminate neonatal tetanus. After Tdap was licensed for use in pregnant women, vaccine manufacturers set up registries to collect safety information on women who had received Tdap during pregnancy. As Healy (2016) summarizes, the data available prior to the 2011 US ACIP recommendation was sufficient for the US to become the first country to recommend Tdap immunization in pregnancy.[12]

Evidence regarding the safety of pertussis vaccination in pregnancy is increasing. From observational vaccine safety surveillance data, no safety signals of concern have been identified to date in the US where vaccination in pregnancy has been recommended since 2011, with uptake estimated at 48.8% of women who had a live birth in 2016.[13]

Since 2011, several randomized clinical trials have assessed Tdap safety in pregnant women. A US phase 1 randomized double blind placebo controlled study of 48 pregnant women (33 received Tdap, 15 did not) found injection site reactions and malaise/myalgia to be the most predominant symptoms following immunization, with no serious adverse events (SAE) reported in any study participant.[14] A randomized controlled trial from Vietnam which compared 52 women who received Tdap with 51 women who received tetanus-toxoid vaccine in pregnancy found adverse events post vaccinations occurred in similar proportions for both groups and no Tdap SAEs occurred.[15] A randomized controlled trial of 204 pregnant women in Mexico demonstrated Tdap safety with the predominant adverse event being localized pain.[16] A large UK cohort study involving data from 20,074 vaccinated women did not find an association between vaccine and poor pregnancy outcomes or adverse events in infants.[17]

The US provides ten years of passively reported Vaccine Adverse Event Reporting System (VAERS) data[18,19] and eight years of actively reported longitudinal US Vaccine Safety Datalink (VSD) data.[20] As summarized by Healy (2016), all but one report found no difference in risk of any adverse pregnancy or

neonatal events. One study of more than 7,000 women found immunization during pregnancy to be protective against preterm birth, small for gestational age and neonatal hospitalization rates.[19]

A small increased risk for chorioamnionitis was found in a matched cohort study using VSD data.[20] This finding led to a focused study by the US CDC of VAERS data, which found a very small number of chorioamnionitis cases in women following Tdap vaccination, however most had at least one pre-existing risk factor.[21] Most recently, a large US cohort study of 1,079,034 deliveries found that Tdap immunization in pregnancy was associated with a small increased relative risk of maternal outcomes, including chorioamnionitis [RR=1.11, (95% CI: 1.07 to 1.15)] and postpartum hemorrhage [RR=1.23 (95% CI: 1.18 to 1.28)].[22] It is of note that chorioamnionitis is a challenging diagnosis and there is limited biologic plausibility for causation, so the clinical value of this finding is unknown. Vaccination with Tdap in pregnancy has not been found to have an association with adverse infant outcomes, which has been studied in both the large US cohort study, and in a study of 197,564 pregnancies by DeSilva et al. (2017).[22,23] As chorioamnionitis increases risk for preterm birth, neonatal infections and pneumonia, DeSilva et al (2017) compared the risk for these infant outcomes between infants of mothers who received Tdap during pregnancy and infants born to unvaccinated women. No increased risk was found for infants born to vaccinated women, further supporting the safety of maternal Tdap vaccination for infants.

A recent systematic review has been published that supports the safety of pertussis vaccination in pregnancy.[24] Careful follow up and safety surveillance is accumulating evidence of safety, based on a growing number of women who have received pertussis vaccination in pregnancy. However, some authors have raised concerns that it is hard to demonstrate safety of a vaccine in pregnancy because it requires very large studies to exclude rare events. De Serres and Skowronski (2017) also highlight that the required sample size to detect a meaningful risk associated with vaccination is especially high when the outcome of interest is frequent in the unvaccinated population, for example, for premature birth which has a baseline risk of approximately 9%.[25] The safety studies by Layton et al. (2017) and DeSilva et al. (2017) were very large, within the range of sample size that De Serres and Skowronski indicated is needed to identify adverse outcomes which may be associated with vaccine, which addresses previous questions about the size of study needed to examine maternal Tdap vaccination risk. Ultimately the issue of unknown safety events that are so rare that they are hard to detect has to be balanced against the known risks of pertussis in young infants and the benefits of vaccination.

The Ontario context

Burden of disease in Ontario

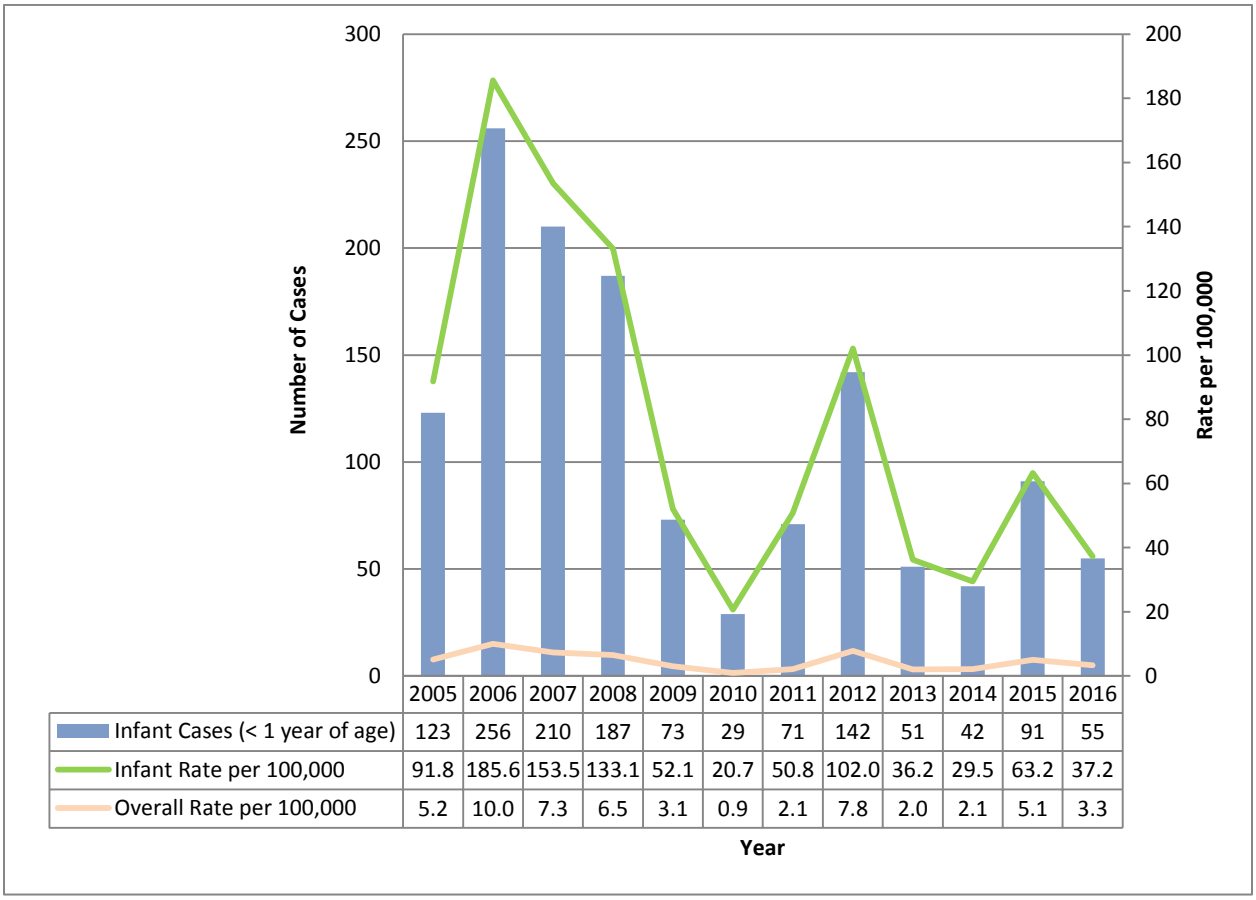
Epidemiology of pertussis in Ontario

Pertussis follows a cyclical trend with peaks occurring every two to five years. Figure 1 demonstrates the Ontario rates for infant pertussis cases and overall cases per year from 2005 to 2016 using data from Ontario's integrated Public Health Information System (iPHIS). Peaks in incidence occurred in 2006 and again in 2012. Note that 2006 was a year in which an unusual outbreak occurred in Toronto during which many asymptomatic children and infants were investigated for pertussis and is likely not representative.[27]

In 2016, 463 cases of pertussis were reported (confirmed and probable) in Ontario, 55 of whom were infants less than one year of age. In 2016, the Ontario infant rate was 37.2 cases per 100,000 population per year compared with an overall rate of 3.3 cases per 100,000 population.

In infants, incidence rates are highest in newborns in the first two months of life (Figure 2); this age group is not yet eligible for pertussis immunization as the first dose of the primary series is given at two months of age. Of the 55 infant cases in 2016, 32 (58%) occurred in infants less than 6 months of age with 22 (40%) occurring in infants less than 2 months of age.

Figure 1: Incidence of pertussis in Ontario, infants and overall, 2005-2016

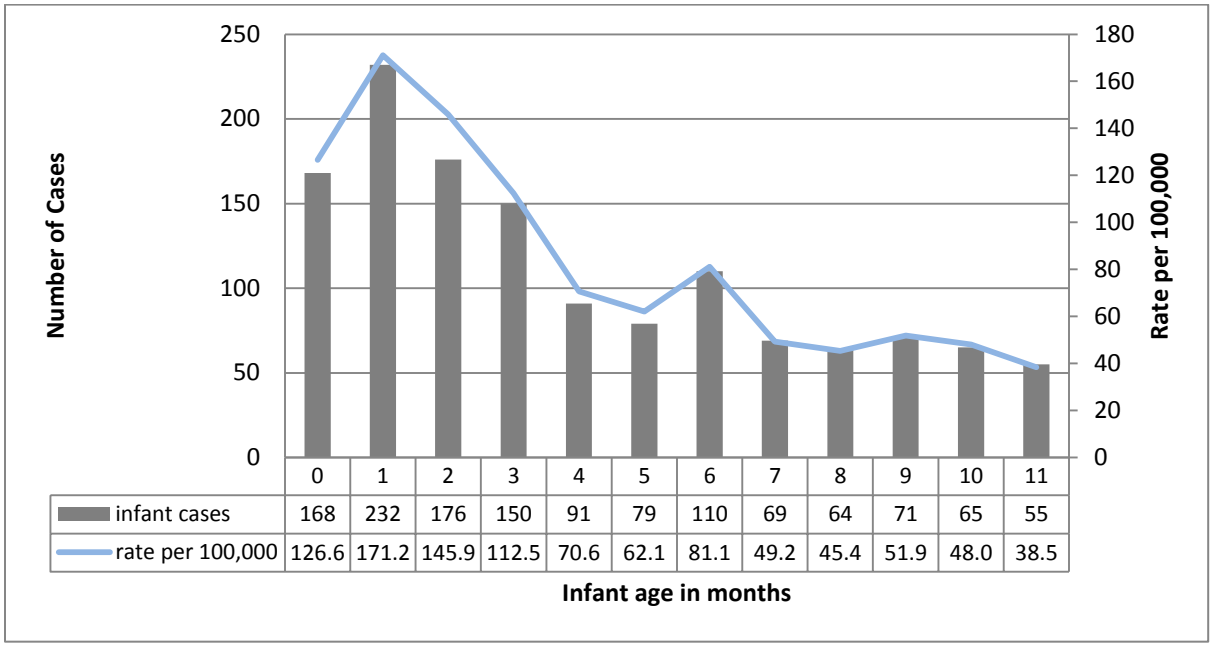


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Infant Cases (< 1 year of age)	123	256	210	187	73	29	71	142	51	42	91	55
Infant Rate per 100,000	91.8	185.6	153.5	133.1	52.1	20.7	50.8	102.0	36.2	29.5	63.2	37.2
Overall Rate per 100,000	5.2	10.0	7.3	6.5	3.1	0.9	2.1	7.8	2.0	2.1	5.1	3.3

Ontario Cases: Ministry of Health and Long-Term Care (MOHLTC), integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2017/06/20].
Ontario Population: Population Estimates [2005-15], Statistics Canada, distributed by MOHLTC, received [2017/02/01]. Population Projection [2016], Statistics Canada , distributed by MOHLTC, extracted [2017/02/01].
Note: Case counts include confirmed (2005-16), epi-linked confirmed (2005-16) and probable (2009-16) cases.

Several changes to pertussis surveillance have been implemented since 2006 including changes to: the diagnostic method to increase specificity; reporting of laboratory results to public health units removing indeterminate results; case definitions;[28] and instructions for follow up to dissuade clinicians from testing asymptomatic contacts.[29,30] Nevertheless, although the rates vary, the pattern of highest incidence being observed for infants less than three months of age is consistent in all years included in the graph (Figure 2).

Figure 2: Incidence of Pertussis in Ontario infants, by month of age, 2005-2016



	0	1	2	3	4	5	6	7	8	9	10	11
infant cases	168	232	176	150	91	79	110	69	64	71	65	55
rate per 100,000	126.6	171.2	145.9	112.5	70.6	62.1	81.1	49.2	45.4	51.9	48.0	38.5

Ontario Cases: Ministry of Health and Long-Term Care (MOHLTC), integrated Public Health Information System (iPHIS) database, extracted [2017/06/20].
Ontario Population: Population Estimates [2001,2006,2011], Statistics Canada, distributed by MOHLTC, received [2017/02/01]. Population Projection [2016], Statistics Canada , distributed by MOHLTC, extracted [2017/02/01]. Population by month of age for years between census years have been annualized.
Note: Case counts include confirmed (2005-16), epi-linked confirmed (2005-16) and probable (2009-16) cases.

No deaths in pertussis cases have been reported in the time period 2006-16, however, in 2017, one death was reported. Approximately two deaths per year from pertussis are reported in Canada; with approximately 40% of the population, Ontario would expect one death from pertussis to occur every year or two. Under-reporting is possible, since deaths can be coded to non-specific or other causes.[26]

Under-reporting of pertussis in Ontario

Pertussis is well-known to be under-reported for a number of reasons including lack of clinical suspicion and lack of testing. In order to explore the potential for cases in infants to be missed by routine reporting, a capture-recapture analysis was conducted as part of the Canadian Immunization Research Network (CIRN) Pertussis Vaccine Effectiveness study.[31] The capture-recapture analysis used data from the time period December 7, 2009 to March 31, 2015 and compared confirmed and probable cases in infants reported in iPHIS with Public Health Ontario (PHO) laboratory confirmations and Canadian Institutes for Health Information (CIHI) hospitalization and emergency department data for Ontario. Data were linked together at the Institute for Clinical Evaluative Sciences (ICES). In the study time period, 337 infant cases were reported in iPHIS. The result of the analysis gives an estimated "true" total of 924 infant cases during that time period (95% CI: 786 to 1126).

Cost-effectiveness of pertussis vaccination in pregnancy

Literature on cost-effectiveness in high income countries

Economic evaluations should be assessed as part of the decision-making process around maternal pertussis immunization. As more jurisdictions have considered maternal pertussis immunization programs, several studies have been conducted to examine the cost-effectiveness of such programs. Emerging evidence from other high-income countries such as the US, England, Spain and the Netherlands have concluded that maternal pertussis immunization is cost effective in their respective settings, however assumptions and cost-effectiveness thresholds have varied widely.

Studies conducted in the US have found maternal immunization during pregnancy to be more cost-effective than both post-partum immunization and cocooning. Cocooning refers to the strategy in which all family members who will be in closest contact with a new baby are vaccinated. Atkins et al. (2016) compared the cost-effectiveness of maternal vaccination, compared to no parental vaccination, mother postpartum, both parents' antepartum or both parents postpartum.[33] The study used a 3% discount rate over a 20 year time horizon and assumed 75% uptake for maternal vaccination. They used an age-stratified transmission model, incorporating empirical data on US contact patterns and modelled parent-infant exposure. They found an incremental cost-effectiveness ratio (ICER) of $114,000 per quality adjusted life year (QALY) (95% prediction interval: $82,000-$183,000, where a prediction interval is similar to a 95% confidence interval) for maternal immunization during pregnancy, which is considered cost-effective by WHO criteria, based on the willingness-to-pay threshold of three times the per-capital gross domestic product (below $159,429 for the US at the time of the study).

Terranella et al. (2013) also examined the economic favourability of maternal pertussis vaccination during the third trimester, compared to a post-partum dose and cocooning in the US.[34] They used National Notifiable Diseases Surveillance System (NNDSS) data to estimate incidence and expected infant cases, and coverage at 72% based on current uptake of maternal vaccines. They further assumed vaccine effectiveness to be 85%, that transfer of maternal antibodies is 100%, and effectiveness in the infant is 60%. The study used a cost of $37.60 plus $20 administrative fee per dose of vaccine and a 3% discount rate of both costs and benefits. They found that vaccination during pregnancy was substantially more cost-effective, at a cost of $414,523/QALY gained, than postpartum vaccination at $1,172,825/QALY gained and cocooning at $2,005,940/QALY. They also estimated a cost of $497,856 per life year saved by maternal immunization during pregnancy, compared to $1,568,164 per life year saved for post-partum vaccination and $2,629,309 for cocooning.

The UK introduced a universal maternal pertussis vaccination program in 2012, and post-implementation economic evaluations have found the program to be cost-effective.[35] Van Hoek et al. (2016) considered the cost of illness to both children and adults, based on National Health Service (NHS) reference costs in 2012-2013, from a health care payer's perspective in England. The study evaluated four different time horizons - 5 years, 10 years, 30 years and 200 years - and assumed vaccine price was £10 or £15, plus £7.50 administration costs per dose. They further assumed 89% (95% CI: 19% to 99%) vaccine efficacy for mothers and 91% (95% CI: 84% to 95%) for infants, a cost and QALY discount rate of

3.5%, and vaccine coverage of 60%. Based on these assumptions, the study predicted the annual costs of the program to be £7.3 million (assuming a price of £10 per dose), which would prevent 1650 hospitalizations in infants (10 year time horizon), 55-60 deaths and about 20,500 cases among mothers. Projecting forward, the study suggests that if pertussis incidence were to remain at the peak 2012 level in England, the immunization program would be highly cost-effective with an ICER of £16,865/QALY (95% Credibility Interval £12,209 to £25,976, where a credibility interval is similar to a 95% confidence interval). These results depend highly on future incidence of pertussis, and 2012 was an exceptional epidemic year in the UK. In most other scenarios modelled with pertussis incidence at non-outbreak levels, the program was not cost-effective.

Fernandez-Cano et al. (2015) provide evidence from Spain, estimating the cost-benefit of maternal immunization during the third trimester (29-36 weeks of gestation) of pregnancy, compared to cocooning, from a healthcare system perspective.[36] The study assumed 85% vaccine effectiveness in mothers at the time of delivery and 60% in neonates during the first two months of life, over a one year time horizon. Their study determined the number needed to vaccinate (NNV) to be 1331 pregnant women to prevent one hospitalization and 200,000 to prevent one death. They found the benefit-to-cost ratio to be 0.15 for vaccination during pregnancy. They conducted a sensitivity analysis using 10% and 90% effectiveness, as well as high and low incidence settings. The results found that immunization during pregnancy was more favourable than cocooning in terms of NNV and net benefit-to-cost ratio for reducing hospitalizations and death in infants under the age of one year. The absolute risk reduction for hospitalizations was found to be 75.2/100,000.

Two studies have compared the cost-effectiveness of pertussis immunization strategies in the Netherlands.[37,38] Westra et al. (2010) compare the cost-effectiveness of three pertussis immunization strategies in the Netherlands: immunizing newborns, cocooning, and maternal immunization during pregnancy.[37] They estimated costs and health benefits in QALYs from both a payer and a societal perspective over a ten-year time horizon. The study assumed 75% vaccine coverage, 89% vaccine effectiveness and standard Dutch discounting rates of 4% for cost, and 1.5% for life years gained. The study found both maternal immunization during pregnancy and cocooning were cost-effective from a payer's perspective at US $4900/QALY (€3500/QALY) and $6400/QALY (€460/QALY) respectively. They further found the immunization program to be cost-saving from a societal perspective, with savings up to $7000 (€7200) for maternal immunization during pregnancy and $10,100 (€5000) for cocooning. Assuming no underreporting of pertussis (which may not be realistic), they found an ICER of $114,200/QALY (€81,600/QALY) for maternal immunization and $296,700/QALY (€211,900) for cocooning, from a payer's perspective. The authors state that the intervention remained cost-effective even considering a 20-30-fold increase in incidence to account for potential underreporting. They concluded that that maternal immunization during pregnancy is cost-effective or even cost-saving in the Netherlands.

Lugner et al. (2013) also investigated the cost-effectiveness of the same three strategies in the Netherlands: immunizing newborns, cocooning, and maternal immunization during pregnancy.[38] They took a societal approach, including costs for health care utilization, productivity losses, and impact on quality of life. They calculated their estimates based on a 10-year vaccination program, assuming that

vaccine-induced immunity lasts 5 years, cost discounting at 4% and discounting life years gained at 1.5%. For maternal immunization during the third trimester of gestation, they assumed vaccine effectiveness to be 90% and vaccine uptake to be 75%. The number of notified cases in newborns and mothers provided the estimate for the number of preventable cases, and death registrations provided the estimate of an average of 0.2 deaths annually. Costs were calculated to include direct health care costs of vaccination and of treatment of disease, and estimated total costs at $3.0 million per year. The study used Health Related Quality-of-Life (HRQoL) weights for pertussis infection, in combination with the length of disease to calculate QALYs, and included life-years lost due to deaths as average life-expectancy at birth of 80.6 years (discounted to 46.8 years). The authors found cocooning to be the most cost-effective option at €89,000/QALY. Maternal vaccination during pregnancy yielded an ICER of about €126,000/QALY. They concluded that neither approach were cost-effective with their base assumptions, or even if incidence were to increase; only in sensitivity analyses using the most favourable assumptions would immunization in pregnancy become cost-effective.

Summary of cost-effectiveness of pertussis vaccination in pregnancy

Overall, cost-effectiveness results are highly influenced by incidence, healthcare and public health system characteristics, cost of vaccine, under-reporting of pertussis, effectiveness of preventative strategies and modeling of herd immunity, all of which make economic evaluations of pertussis immunization programs difficult to conduct and compare with accuracy.[39] There is wide variation in the assumptions underpinning the cost-effectiveness estimates found, which is demonstrated in Table 1. Table 1 also summarizes the key findings of the included studies. It highlights the difficulty in making comparisons across studies since the context, currencies and time periods vary. It is most notable that all but one study found maternal immunization during pregnancy to be a more cost-effective strategy than post-partum immunization and cocooning. The exception found cocooning to be more cost-effective than maternal immunization, but in neither case were estimates below accepted thresholds.[38] ICER estimates ranged from £16,865/QALY[35] to $414,532/QALY.[34] Of the studies examined, only two found cost-effectiveness results to be below the generally accepted threshold in Canada of $50,000/QALY (Canadian dollars). Despite these limitations and broad range of estimates, authors of the studies that have been conducted in high-income countries have generally concluded that maternal pertussis immunization during pregnancy is cost-effective. However, some of the thresholds used in other countries are above what would be considered cost-effective in Canada. The costs of healthcare also vary widely – being extremely high in countries such as the US, with a for-profit healthcare industry, which tends to make vaccination appear more cost-effective. In comparison, caring for infants with pertussis is much less expensive in countries such as the UK and the Netherlands that publicly fund healthcare. Vaccine costs are also often lower in those settings because of centrally negotiated contracts. Ontario's publicly-funded healthcare system includes central funding and procurement of vaccines but has features that may make care in Ontario more expensive and less cost-efficient, including fee-for-service clinician payments and non-salaried independent hospital specialists.

Pertussis incidence is a key driver of cost-effectiveness. For example, the UK study found their program to be cost-effective only if they assumed that the peak incidence in 2012 of 18 cases per 100,000 population for all age groups in England would be sustained. This was the largest outbreak in infants and

highest incidence observed for more than a decade.[39] The incidence observed in the UK in 2012 is considerably higher than the average incidence in Ontario during the period 2012-2016 (including an epidemic year in 2012) of only 3.8 per 100,000.[40] Further analysis is needed to address whether pertussis vaccination in pregnancy would be cost-effective in Canada, including in Ontario. One key aspect that supports cost-effectiveness in Ontario is that a dose of vaccine is already funded for all adults which potentially covers the cost of one dose for pregnant women, noting that the average number of children is approximately two. Administration costs would be an important issue to consider in an Ontario-specific analysis.

Table 1: Summary of Cost-Effectiveness Literature from High Income Countries

Country	Author	Assumptions	Results
US	Atkins et al. (2016)	Coverage: 75% Vaccine Effectiveness: varied by dynamic modelling Efficacy of maternally acquired antibodies: 89% Discount Rate : 3% Time Horizon: 20 years Cost of vaccine dose: $21 + $23 administrative fee	ICER: $114,000/QALY
US	Terranella et al. (2013)	Coverage: 72% Vaccine Effectiveness in mothers: 85% Vaccine Effectiveness in infants: 60% Discount Rate : 3% Time Horizon: 1 year Cost of vaccine dose: $37.60 + $20 administrative fee	ICER: $414,523/QALY LYS: $497,856

Country	Author	Assumptions	Results
England	Van Hoek et al. (2016)	Coverage: 60% Vaccine Effectiveness in mothers: 89% Vaccine Effectiveness in infants: 91% Discount Rate : 3.5% Time Horizon: 5, 10, 30 and 200 years Cost of vaccine dose: £10 or £15 + £7.50 administrative fee	ICER: £16,865/QALY
Spain	Fernandez-Cano et al. (2015)	Coverage: 60% Vaccine Effectiveness in mothers: 85% Vaccine Effectiveness in infants: 91% Efficacy of maternally acquired antibodies: 60% Time Horizon: 1 year Cost of vaccine: €8 + €9 administrative fee	NNV to prevent 1 hospitalization: 1331 NNV to prevent 1 death: 200,000 Benefit-to-cost-ratio: 0.15
Netherlands	Westra et al. (2010)	Coverage: 96% Vaccine Effectiveness : 89% Discount Rate: 4% costs, 1.5% life years gained Time Horizon: 8 years Cost of vaccine: €25.60 +€8.40 administrative fee	ICER: €4900/QALY

Country	Author	Assumptions	Results
Netherlands	Lugner et al. (2013)	Coverage: 75% Vaccine Effectiveness in mothers: 89% Discount Rate : 4% costs, 1.5% life years gained Time Horizon: 10 years Cost of vaccine dose: €27	ICER: €126,000/QALY

Acceptability considerations

Although experience of pertussis immunization in pregnancy has been encouraging in other countries, it is unclear yet whether it will be acceptable in Canada. The programs in the UK and US were implemented in the context of highly publicized pertussis outbreaks that involved hospitalizations and deaths of infants. This likely had an effect on acceptability in those countries. In Canada, pertussis incidence is currently relatively low, with only one death reported in Ontario over many years. Questions remain about whether women in Ontario will agree to be vaccinated, and whether health care providers will be supportive.[42,43] As an example of acceptance of vaccination in pregnancy, uptake of influenza immunization in pregnancy is very low.[44] A CIRN-funded maternity care provider survey collected data in the summer of 2017 in collaboration with The Society of Obstetricians and Gynecologists of Canada. Information about the attitudes, knowledge and practices of maternal vaccinators was collected, which will be useful in informing maternal pertussis vaccination implementation. The potential to gain synergistic benefits from promoting influenza vaccination in pregnancy with pertussis vaccination is worth exploring further.

Feasibility considerations

Additional work is needed to determine the feasibility of successfully implementing a recommendation to immunize in every pregnancy. Lessons from the experience of implementing influenza vaccination in pregnancy are instructive; influenza immunization coverage in Canada is low at approximately 25% [45] compared with the US (~54%)[46] and the UK (~40%)[47].

Obstetricians attended the delivery of 84% of infants in Ontario in 2013/14 based on data from the Better Outcomes Registry Network (BORN) data.[48] The proportion delivered by an obstetrician may over-estimate the proportion that get antenatal care solely from an obstetrician because some would have been cared for during pregnancy by their family practice or midwife and then had a transfer of care to an obstetrician during labour for a medical reason. Obstetricians may not have the required infrastructure to vaccinate women, including vaccine fridges for storage, and may not routinely access

publicly-funded vaccines. Midwives may need to have Tdap immunization added to their scope of practice (which currently includes hepatitis B and MMR vaccines.[49] Anecdotally, it is common practise for obstetricians to refer pregnant women to their family doctor for immunization. Referring these women to their family doctors for immunization however places an additional barrier to access to vaccines. It is unknown how much this contributes to the low uptake of influenza vaccination in pregnancy in Ontario.[42,43] Pharmacists may be a more feasible alternative for easy access to maternal vaccinations during pregnancy, if it can be included in their scope of practice. Addressing the feasibility issues for pertussis vaccination may have additional benefits in promoting uptake of influenza vaccine in pregnancy as well.

The recommended optimal timing of pertussis immunization in pregnancy may have practical considerations for whether it is delivered by primary care providers (including family physicians), pharmacists, obstetricians or midwives. Early in pregnancy, women may be cared for by their primary care physician, but later on they may be referred to obstetricians.

Equity considerations

Inequity may result from lack of access to a healthcare practitioner, or inability to pay for vaccine in the absence of a publicly-funded program for pregnant women. Currently a single recommended dose of pertussis vaccine for adults is funded in Ontario. This would provide free access to pregnant women who have not yet had an adult dose on a one-time basis only. Universally-funded pertussis immunization during each pregnancy would increase equity of access to protection from pertussis for Ontario infants.

Conclusions

Pertussis immunization in pregnancy appears to be safe and effective and is now recommended by NACI as well as immunization advisory committees in other high-income countries, including Australia, the UK, and the US. NACI recommendations for pertussis immunization in pregnancy are supported by published evidence and are applicable in the Ontario context.

Whilst the cost-effectiveness of immunizing in pregnancy is less clear, the high effectiveness of this approach is completely aligned with the primary goal of the pertussis immunization program to prevent severe disease and death in infants.

Cost-effectiveness, acceptability, feasibility, and equity are considerations in informing policy decisions in in Ontario.

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