

## CANADIAN RESEARCH PRIORITIES FOR PERTUSSIS IMMUNIZATION IN PREGNANCY SURVEY

### Background

Pertussis immunization in pregnancy is currently thought to be the most effective way of protecting young infants (<3 months of age) against pertussis, in conjunction with an immunization program for children. The National Advisory Committee on Immunization (NACI) has recently recommended pertussis immunization for all pregnant women in Canada during every pregnancy. The PIPER (Progressing Immunization in Pregnancy Evaluation and Research) Group was established to bring together individuals with expertise and/or interest in this area and to develop a cohesive roadmap for evaluation and research on immunization in pregnancy in Canada. At a PIPER workshop in May 2017 attended by 34 immunization experts across Canada, 39 specific evidence gaps around **pertussis immunization in pregnancy** were identified by consensus. To help prioritize these gaps for future research, a survey was sent to diverse Canadian immunization research and evaluation stakeholders inclusive of those that attended the workshop (Appendix 1). These stakeholders were researchers (e.g., scientists, clinician-scientists), decision makers (e.g., provincial and local policy makers), end users (e.g., program managers, physicians, midwives) and funders (including industry and non-industry funders).

### Methods

A cross-sectional survey was developed based on items generated at the workshop. Invitations to the web-based survey were sent to 153 Canadian stakeholders identified by workshop participants as having experience, interest and/or expertise in this field. The survey was open between January 19 and February 21, 2018. The Qualtrics 2018.03 survey platform was used as per the site license of the University of British Columbia.

Respondents were asked to self-identify their expertise level in immunization in pregnancy as beginner, novice, intermediate, proficient or expert. For each evidence gap respondents used a 5-point Likert Scale to rate (1) importance to have **new research to fill the evidence gap**, relevant to pertussis immunization in pregnancy in Canada and (2) feasibility of **new research** in this area in Canada. It was emphasized that the rating was based on new research in Canada. The evidence gaps covered 5 different populations: (i) pregnant women; (ii) all women of child bearing age; (iii) newborns/infants age <3 months; (iv) maternity care providers; (v) existing frontline immunization providers. Respondents were also able to add any additional gaps in free text fields.

The Likert scale ranked importance/relevance of each evidence gap on a scale from 0-5, defined as: 0=no opinion; 1= not important/relevant; 2= low importance/relevance; 3=somewhat important/relevant; 4= high importance/relevant; 5=very high importance/relevance.

Feasibility of conducting new evaluation or research into the identified evidence gap was ranked on a scale from 0-5 using the following definitions: 0=no opinion; 1= not feasible; 2= feasible but will be difficult to conduct; 3= may be feasible in some settings; 4= generally feasible; 5=very feasible.

Survey participants were provided the opportunity to opt out of part of or the entire survey. The mean score for importance and feasibility of each evidence gap was calculated using SAS, including data from all participants who responded to that question with a score between 1 and 5. Go Zone scatter plots were generated by plotting the mean ranking of importance and feasibility for each question, using Microsoft Excel. Separate Go Zone plots were also constructed by categorized primary role in immunization to allow for examination of the different needs and perspectives of researchers, end-users, decision-makers and funders of research. Participation in the survey was assumed to imply consent. Differences in rankings between groups were estimated by calculating the intraclass correlation coefficient (ICC) separately for importance ranking and feasibility ranking.

## Results

Of the 153 individuals invited to complete the survey 71 responded (Table 1). For survey respondents their self-reported primary role and level of expertise was used. For non-respondents their primary role in immunization was determined by review of their participation in immunization stakeholder committees, work and/or publications. Of respondents, 35 were physicians (16 pediatric infectious diseases, 13 public health, 3 obstetric, 3 other), 20 self-identified as scientists/researchers (9 with expertise in epidemiology, 5 immunology, 2 social science, 4 other), 6 were allied health care providers, 6 program managers, and 4 were other/unknown.

**Table 1: Survey Invitees and Respondents by their Primary role in Immunization and Level of Expertise**

	<b>Total, N</b>	Researcher, N	End User, N	Decision- maker, N	Funder*, N	Other/Unknown/ Missing, N
Survey Invites sent	<b>153</b>	93	37	10	10	3
Completed & partially completed surveys	<b>71</b>	44	13	6	5	3
Respondents level of expertise	<b>20</b>	10	5	1	2	2
Beginner/Novice Expertise	<b>22</b>	14	3	3	2	0
Intermediate	<b>29</b>	20	5	2	1	1
Proficient/Expert						

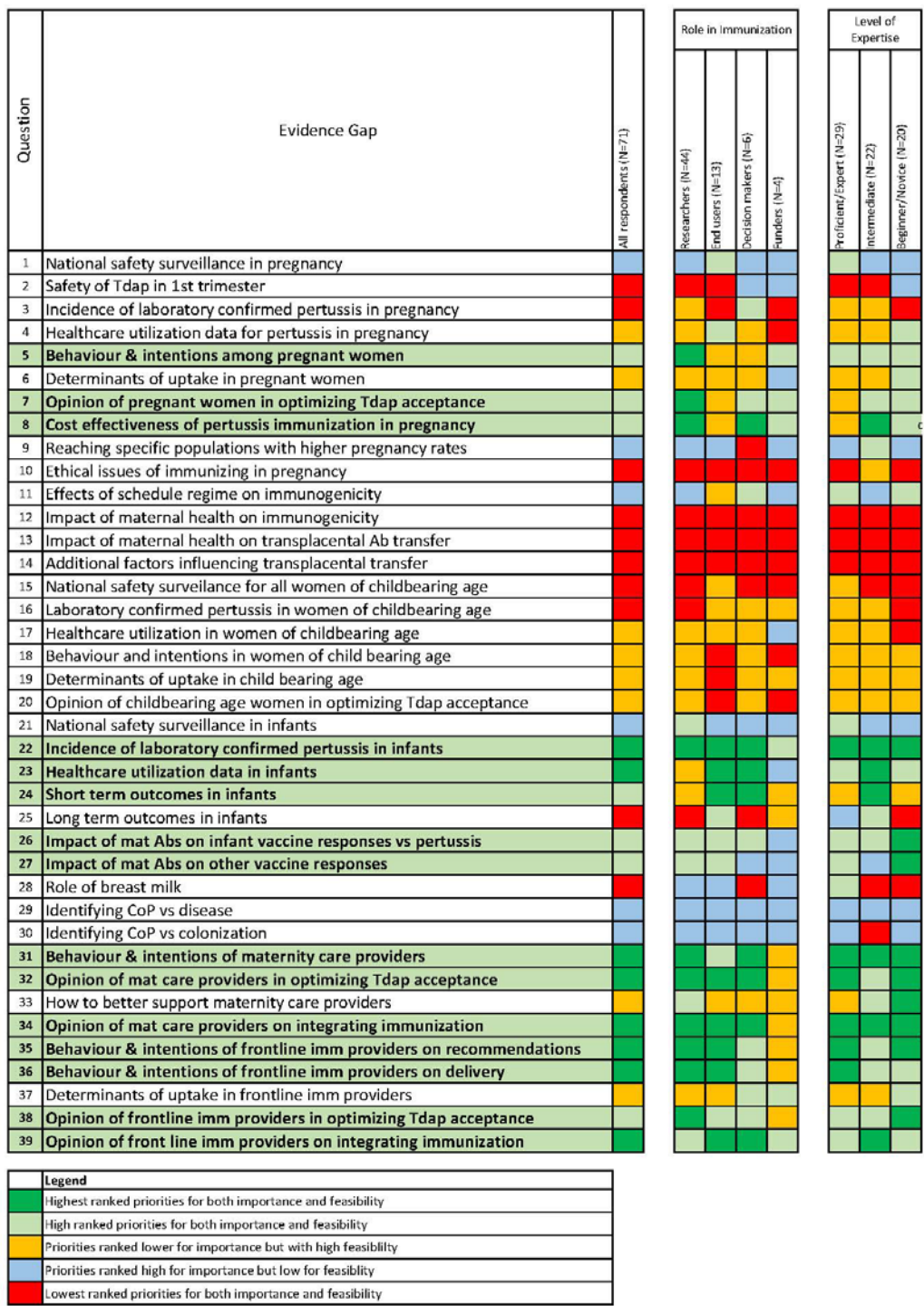
\*including industry or grant funders

Each of the 39 evidence gaps ranking of importance/relevance and feasibility for the research to be conducted in Canada was ranked relatively high. The mean importance ranking ranged from 3.1 to 4.4 with 12/39 (31%) gaps having a mean ranking  $\geq 4.0$  (high or very high importance). The mean feasibility ranking ranged from 2.4 to 4.2 with 12/39 (31%) gaps having a mean ranking of  $\geq 4.0$  (generally or very feasible).

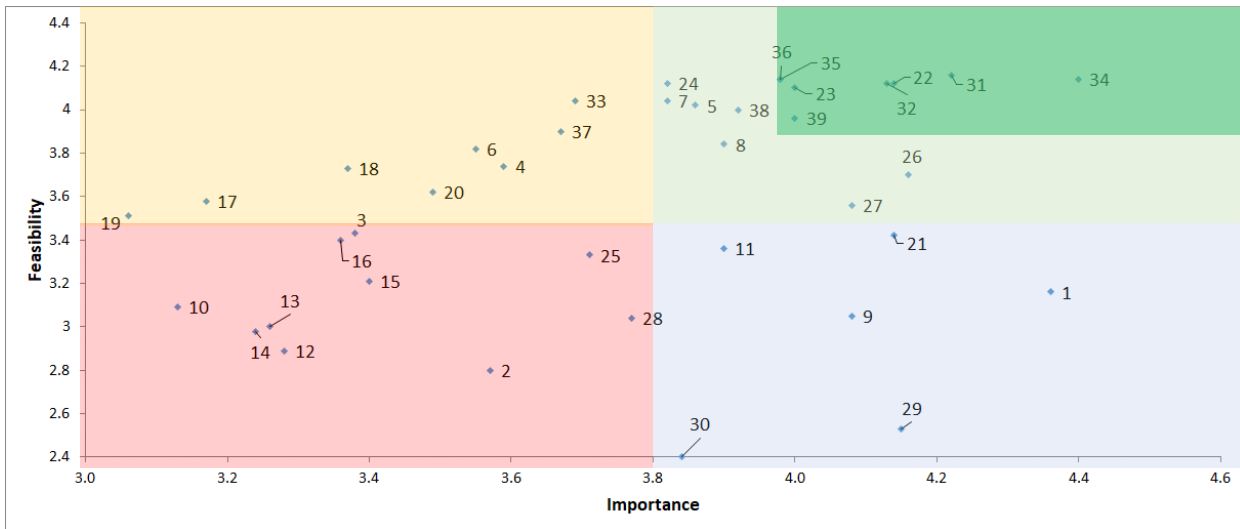
Evidence Gaps 5, 7, 8, 22, 23, 24, 26, 27, 31, 32, 34, 35, 36, 38 and 39 were the most highly ranked overall with regards to combined high importance and feasibility (Figure 1). Of these 15 highest ranked gaps, 9 were broadly related to areas of social science, and 7 of these were focussed on research of healthcare providers (perinatal or immunization care providers). Other gaps ranked highest were in areas of epidemiology, immunology and cost effectiveness. The ICC between responder groups when categorized by primary role was 0.465 for importance (indicating poor agreement between groups) and 0.712 for feasibility (indicating moderate agreement between groups). Overall, the ICC between the three groups based on their expertise was 0.753 for importance and 0.757 for feasibility, indicating good agreement, but there were some differences between respondents who regarded themselves as 'proficient/expert' in this field compared with those self-identifying as beginner to intermediate. Of note, those with higher expertise regarded gap 28 (role of breast milk) higher in terms of importance and feasibility, gaps 1, 15 and 21 (all relating to national safety surveillance) higher in terms of feasibility, and gaps 7, 8 and 33 lower in terms of importance, compared with those with intermediate/lower expertise (Figure 1).

Go Zone Plots were constructed (Figures 2 to 6) examining patterns of relative importance vs. feasibility for all respondents, and categorized by primary role.

**Figure 1: Evidence gaps & summary of Go Zones for *all respondents* and by *primary role in immunization* (N=71). Gaps highlighted in green were in the green 'go zone' overall.**

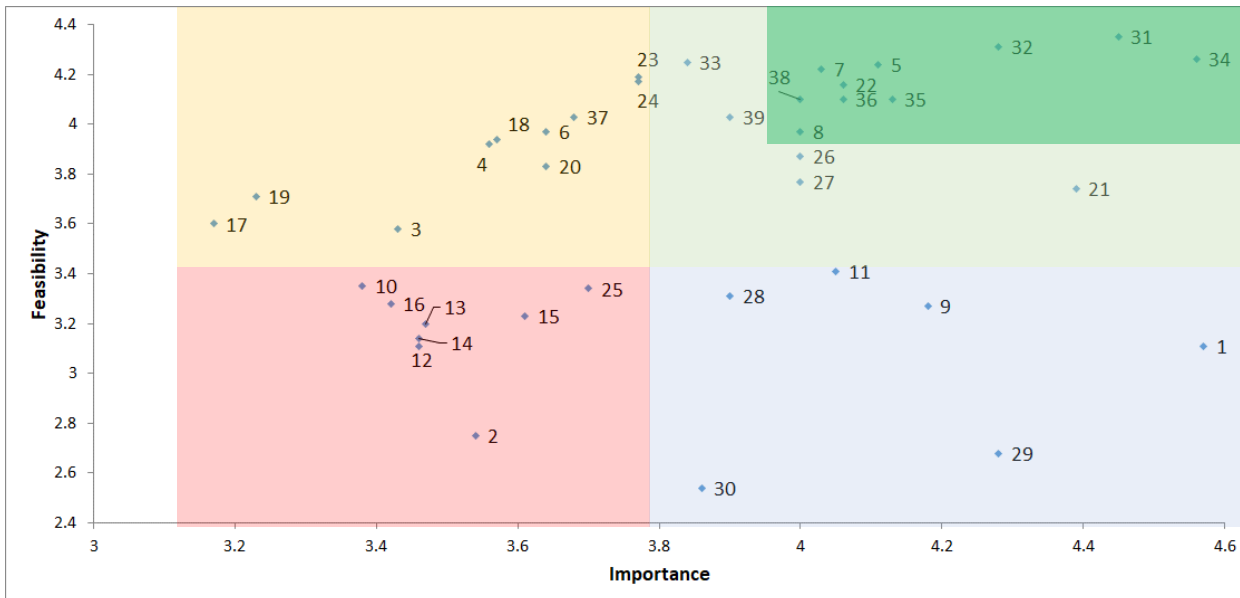


**Figure 2: Go Zone Plot of Importance versus Feasibility rankings by all participants (N=71)**



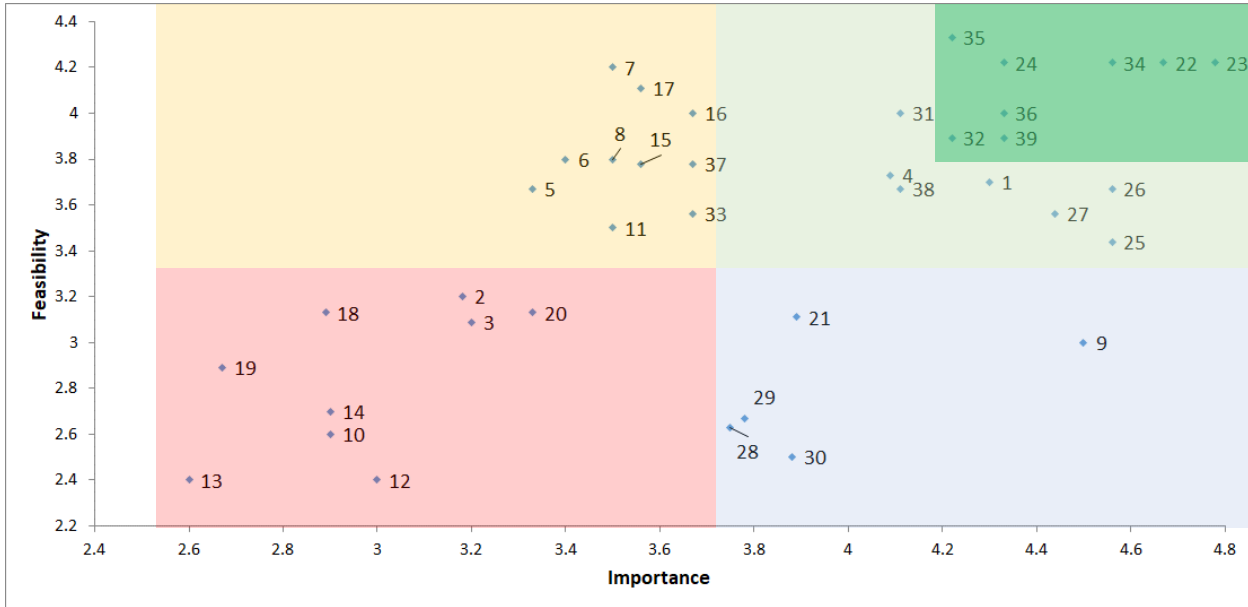
Colours indicate relative ranking. Dark green: highest ranked for both importance and feasibility; green: highly ranked for both importance and feasibility; orange: ranked lower for importance but with high feasibility; blue: ranked high for importance but low for feasibility; red: lowest ranked for both importance and feasibility

**Figure 3: Go Zone Plot of Importance versus Feasibility rankings by researchers (N=44)**



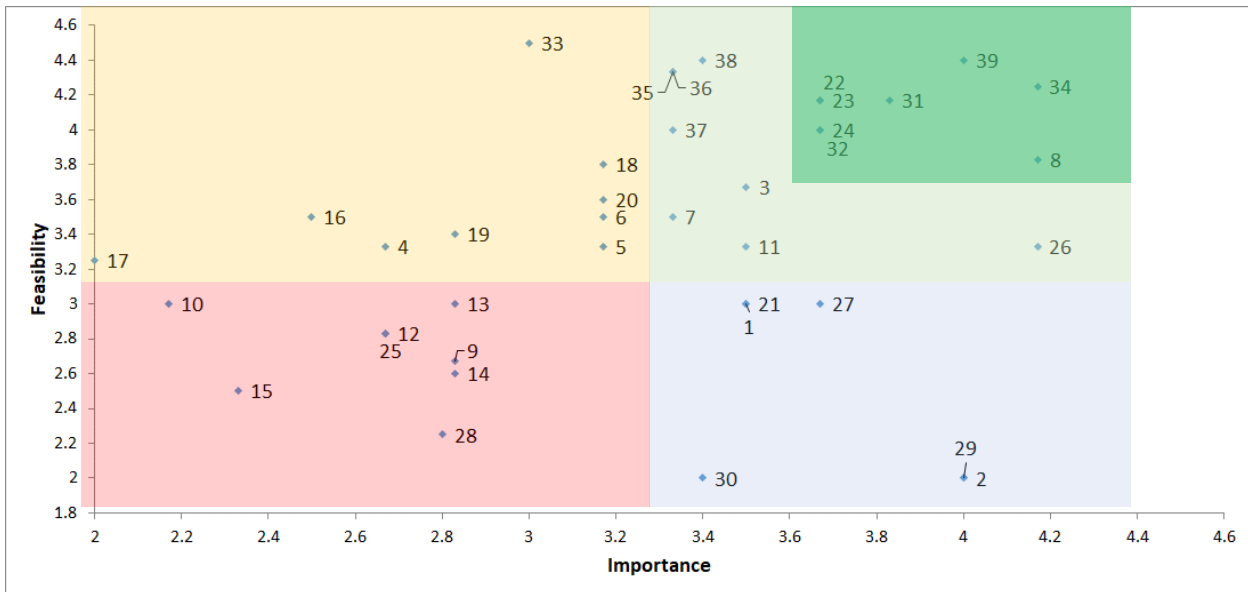
Colours indicate relative ranking. Dark green: highest ranked for both importance and feasibility; green: highly ranked for both importance and feasibility; orange: ranked lower for importance but with high feasibility; blue: ranked high for importance but low for feasibility; red: lowest ranked for both importance and feasibility

**Figure 4: Go Zone Plot of Importance versus Feasibility rankings by end users (N=13)**



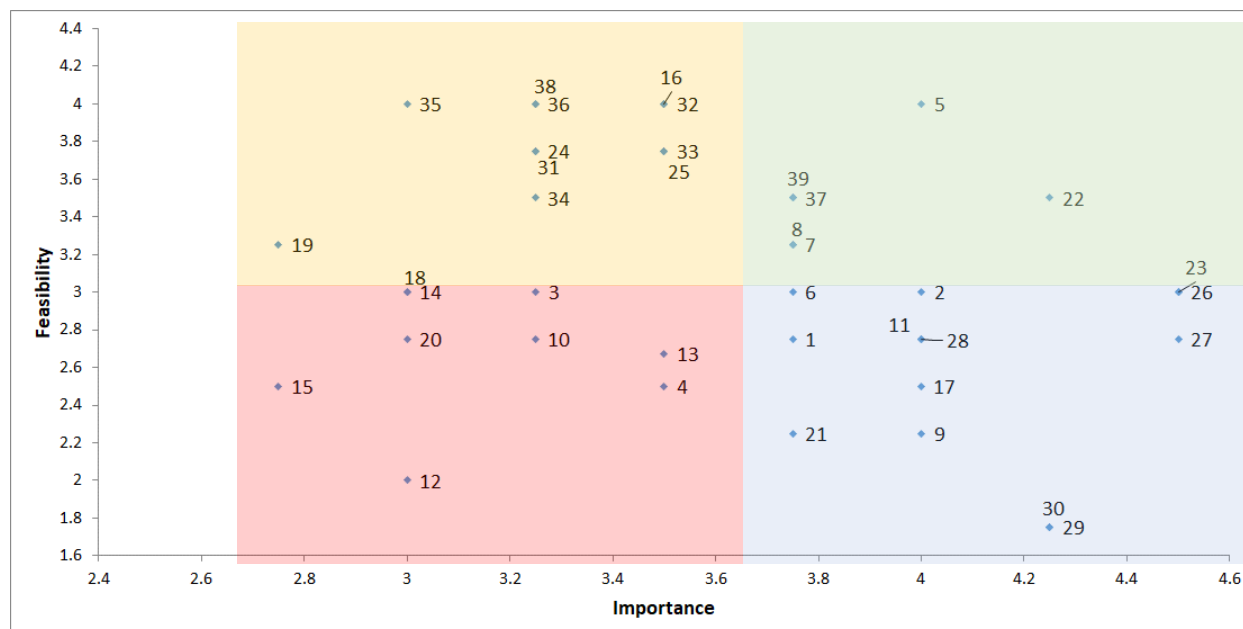
Colours indicate relative ranking. Dark green: highest ranked for both importance and feasibility; green: highly ranked for both importance and feasibility; orange: ranked lower for importance but with high feasibility; blue: ranked high for importance but low for feasibility; red: lowest ranked for both importance and feasibility

**Figure 5: Go Zone Plot of Importance versus Feasibility rankings by decision makers (N=6)**



Colours indicate relative ranking. Dark green: highest ranked for both importance and feasibility; green: highly ranked for both importance and feasibility; orange: ranked lower for importance but with high feasibility; blue: ranked high for importance but low for feasibility; red: lowest ranked for both importance and feasibility

**Figure 6: Go Zone Plot of Importance versus Feasibility rankings by funders (N=4)**



Colours indicate relative ranking. Dark green: highest ranked for both importance and feasibility; green: highly ranked for both importance and feasibility; orange: ranked lower for importance but with high feasibility; blue: ranked high for importance but low for feasibility; red: lowest ranked for both importance and feasibility

The survey also enabled respondents to list additional evidence gaps they felt were not included in the 39 questions, summarized in Table 2.

**Table 2: Other evidence gaps identified by respondents that were not included in the survey**

Impact of multiple different vaccines during pregnancy
Willingness to be vaccinated with multiple different vaccines during pregnancy
Independent assessment of all pertussis clinical trial data
Data of vaccine coverage
Role of media in shaping opinion
Outcomes of immunization during pregnancy on the infant’s response to other vaccines
Effectiveness of cocooning immunization strategy
Need relevant animal models for maternal immunization
Vaccine effectiveness studies in infants

**Discussion**

Overall survey response was good at almost 50% completed and partially completed amongst the 153 who received it. The majority of respondents were researchers and end users, and the results therefore are most reflective of the opinions of these groups. Expertise was spread across the spectrum. Most of the highest priority areas for Canada identified relate to social science and programmatic evidence gaps, with additional epidemiologic and immunologic evidence gaps also considered a high priority. Even those evidence gaps which were ranked lowest were all considered to be at least somewhat important and all considered to be feasible to an extent, with a few regarded as feasible but difficult to conduct or only feasible in some settings. This may reflect a degree of pre-selection of what are already important topics at the workshop. For the highest ranked

gaps there was reasonably good concordance between different stakeholder groups, suggesting that a cohesive approach to address these gaps should be undertaken. Most of the gaps relating to vaccine safety surveillance were regarded as highly important and feasible by those with greater expertise. Some of the gaps relating to understanding pertussis vaccine immunology in pregnancy, even those that were regarded as of highest importance, were not considered as feasible as some of the other gaps. The next steps in this process aimed at development of a cohesive roadmap for future immunization in pregnancy evaluation and research in Canada should include:

1. Detailed face-to-face discussion between all relevant stakeholders including funders and policy-makers to design studies and identify funding to address the highest priorities for pertussis immunization in pregnancy research and evaluation
2. Additional discussion to identify priorities for other issues around immunization in pregnancy
3. Further discussion around feasibility issues and how to bridge the gap to ensure that those evidence gaps thought to be the most important can be made feasible broadly across Canada, and not just limited to specific settings.

### **Acknowledgements**

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**Appendix 1**  
**Evidence Gaps used in the survey**

**Pregnant women given pertussis vaccine.**

1. Establishment of National system(s) to enable safety surveillance for immunizations given during pregnancy, related to adverse events in the pregnant woman and/or fetus
2. Safety of pertussis immunization in the first trimester of pregnancy
3. Determining the incidence of laboratory confirmed pertussis disease in pregnant women
4. Generation of Canadian healthcare utilization data for pertussis disease in pregnant women, e.g. hospitalization rates, length of stay, ICU admission, etc
5. Improved understanding of behaviour and intentions around pertussis immunization in pregnancy among pregnant women
6. Differences in determinants in pregnant women of pertussis vaccine uptake in pregnancy vs. in their infants
7. Understanding opinions of pregnant women on how to optimize pertussis immunization acceptance during pregnancy
8. Cost effectiveness of pertussis immunization in pregnancy
9. How to reach specific populations where pregnancy rates may be higher than the Canadian average, e.g. Indigenous populations, newcomers to Canada
10. Addressing the ethical issues of immunization in pregnancy programs in Canada
11. Effects of immunization regime (e.g. schedule, dosing, timing during pregnancy, repeated immunization in every pregnancy) on vaccine immunogenicity
12. Impact of maternal health (e.g. nutrition, obesity, age, comorbidities) on vaccine immunogenicity in pregnant women
13. Impact of maternal health (e.g. nutrition, obesity, age, comorbidities) on transplacental transfer of maternal antibody
14. Additional factors influencing transplacental transfer of IgG from the pregnant woman to the fetus, e.g. antibody subtype, function

**All women of child bearing age given pertussis vaccine.**

15. Establishment of National system(s) to enable safety surveillance for immunizations given to all women of childbearing age
16. Determining the incidence of laboratory confirmed pertussis disease in all women of childbearing age
17. Generation of Canadian healthcare utilization data for pertussis disease in all women of child bearing age, e.g. hospitalization rates, length of stay, ICU admission, etc
18. Improved understanding of behaviour and intentions around pertussis immunization in pregnancy in all women of child bearing age
19. Differences in determinants in all women of child bearing age of pertussis vaccine uptake in pregnancy vs. in infants
20. Understanding opinions of all women of child bearing age in how to optimize pertussis immunization acceptance during pregnancy

**Newborn/infant (age <3 months) exposed to pertussis vaccine during pregnancy**

21. Establishment of National system(s) to enable safety surveillance for adverse events in infants exposed to maternal pertussis vaccine in utero
22. Determining the incidence of laboratory confirmed pertussis disease in young infants
23. Generation of Canadian healthcare utilization data for pertussis disease in young infants, e.g. hospitalization rates, length of stay, ICU admission, etc
24. Short term (days-weeks) outcomes following pertussis disease in young infants



25. Long term (months-years) outcomes following pertussis disease in young infants
26. Impact of passively transferred maternal antibodies on infant vaccine responses against pertussis
27. Impact of passively transferred maternal antibodies on infant vaccine responses against other vaccines (i.e. tetanus, diphtheria, meningococcal, pneumococcal and Hib vaccines).
28. Role of breast milk in protecting infants against pertussis
29. Identifying a correlate of protection for pertussis against disease in infants
30. Identifying a correlate of protection for pertussis against colonization of the respiratory tract in infants

**Maternity care providers (including midwives, nurses, obstetricians, family doctors) who may either provide or recommend pertussis vaccine during pregnancy**

31. Behaviour and intentions of maternity care providers around pertussis immunization recommendations in pregnancy
32. Understanding opinions of maternity care providers in how to optimize pertussis immunization acceptance during pregnancy
33. Understanding how to better support maternity care providers in providing pertussis vaccine
34. Opinions of maternity care providers as to how best to integrate pre-natal pertussis immunization into routine obstetric care

**All front line immunization providers (including providers of all vaccines, such as public health nurses, pharmacists, family doctors) who may either provide or recommend pertussis vaccine during pregnancy**

35. Behaviour and intentions of frontline immunization providers around pertussis immunization recommendations in pregnancy
36. Behaviour and intentions of frontline immunization providers around pertussis immunization delivery in pregnancy
37. Differences in determinants of vaccine recommendations and/or delivery for pertussis immunization in pregnancy vs. pertussis immunization in infants among frontline immunization providers
38. Understanding opinions of frontline immunization providers in how to optimize pertussis immunization acceptance during pregnancy
39. Opinions of frontline immunization providers as to how best integrate pre-natal pertussis immunization into routine obstetric care