Vaccine 37 (2019) 7138–7146

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Developing product label information to support evidence-informed use of vaccines in pregnancy

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ARTICLE INFO

Article history:
Received 4 May 2019
Received in revised form 18 September 2019
Accepted 19 September 2019
Available online 5 October 2019

Keywords:
Consensus methods
Immunization
Influenza
Pertussis
Pregnancy
Vaccination

ABSTRACT

Background: Product labelling information describing the use of vaccines in pregnancy continues to contain cautionary language even after clinical and epidemiological evidence of safety becomes available. This language raises safety concerns among healthcare providers who may hesitate to recommend vaccines during pregnancy.
Purpose: To develop clear evidence-based language about vaccine safety and effectiveness in pregnancy for inclusion in vaccine product labels.
Methods: We conducted a three-stage consensus-methods project with stakeholders, including: healthcare providers, vaccine regulators, industry representatives, and experts in public health, communication, law, ethics, and social sciences. Using qualitative and quantitative methods, we held a nominal group technique (NGT) meeting, followed by a Delphi survey, and then a consensus workshop with a subset of Delphi participants. We developed a methodological tool to analyse data for consensus.
Principal results: Stakeholders (N = 14) at the NGT meeting drafted product label statements for evaluation in the Delphi survey. Survey participants (N = 41) provided feedback on statements for five hypothetical vaccines. Workshop participants (N = 27) initiated discussions that demonstrated a lack of awareness that the regulatory purpose of product labels is to provide a scientific summary of product-specific preclinical and clinical trial data. Each stage of this project built on earlier stages until we achieved strong consensus on the language, structure, and types of data that stakeholders wanted to include in inactivated influenza vaccine (IIV) and tetanus-diphtheria-acellular pertussis (Tdap) vaccine product labels in Canada.

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https://doi.org/10.1016/j.vaccine.2019.09.063
0264-410X/

Conclusions: The revised statements for IIV and Tdap aligned with workshop participants' goals that the product label be evidence-based, with a consistent structure and language that is easily understood by healthcare providers. Emergent methods uncovered stakeholder concerns about the regulatory purpose, content, and evidence used in product labels. Involving healthcare providers in the development and regular updating of product information could prevent interpretations of that information that contribute to vaccine hesitancy.

1. Introduction

Since 2007, Canada's National Immunization Technical Advisory Group (NITAG), the National Advisory Committee on Immunization (NACI), has recommended routine vaccination during pregnancy with inactivated influenza vaccine (IIV) [1,2]. In February 2018, NACI began recommending tetanus-diphtheria-acellular pertussis (Tdap) vaccination during the third trimester of every pregnancy [1,2]. The safety of IIV and Tdap use in pregnancy is well documented [3–8]. Influenza vaccination during pregnancy can prevent influenza in pregnancy and infancy, and may benefit the fetus [9–11], while Tdap vaccination in pregnancy has shown high effectiveness against pertussis in young infants, the age group with the highest mortality rate [12–14]. NACI recommendations are consistent with evidence-informed recommendations from the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) [3] and NITAG recommendations in several other high-income countries, including the United States (US), United Kingdom (UK), and Australia [15–18]).

In most high-income countries that recommend IIV and Tdap vaccinations during pregnancy, their uptake is low. In the US, vaccine uptake during pregnancy ranges from 20% to 70% for both IIV and Tdap [19,20], while uptake in some regions of the UK is as low as 26% for Tdap and 50% for IIV [21]. IIV uptake among pregnant Canadians is similarly low, around 20% in the province of Nova Scotia and 40% in Quebec [22,23]. At the time of writing, most provinces and territories had only recently implemented Tdap vaccination in pregnancy and uptake in Canada was unknown.

A recommendation from a trusted healthcare provider (HCP) is a strong predictor of IIV and Tdap uptake among pregnant women in Canada and other high-income countries [17,19–21].[2] Yet, HCPs may hesitate to recommend vaccines in pregnancy for several reasons, including concerns about the evidence regarding vaccine safety and effectiveness, and inconsistencies between information sources [26,27].

Two common information sources HCPs consult about vaccine use in pregnancy are: (1) NITAG recommendations for vaccine use in public health programs and (2) vaccine product label information developed by the manufacturer and approved by the National Regulatory Authority (NRA) (commonly referred to as the product monograph or the product label), which includes the vaccine's properties, indications, and contraindications [27,28]. The package insert is the leaflet in the vaccine box that contains a summary of the product label information.

NITAG recommendations provide guidance for incorporating a vaccine into public health programs and appropriate vaccine use in clinical practice. The NITAG review considers the burden and severity of the disease targeted by the vaccine and makes recommendations aimed at maximizing public health benefit. NITAG recommendations are reviewed and updated regularly based on post-market observational studies and vaccine safety surveillance data and are not product-specific [29].

NRA regulations stipulate that manufacturer-developed vaccine product information should provide a non-promotional summary of scientific information about the product and its use based on product-specific pre-clinical and clinical data [30,31]. Disease burden and risk are generally not included in product labelling information in Canada. Because few clinical trials involve pregnant women, information on use in pregnancy included in vaccine product labels is based on more limited evidence than the evidence supporting NITAG recommendations [27,29,32]. Thus, the language in product labels about use in pregnancy is often cautionary [27–29,31,33], and such language has been shown to raise safety concerns among HCPs [27,28]. For example, the product label for an IIV that NACI recommends for use in pregnancy reads: "*The safety of [the vaccine] when administered to pregnant women has not been evaluated*" [34]. Many NRAs, including Health Canada, do not require regular updates of product label information unless a new safety concern arises for the indicated use of a particular vaccine product [35,36] For these reasons, outdated product label information may contradict NITAG recommendations for IIV and Tdap vaccination during pregnancy, which could contribute to vaccine hesitancy. There is a need for product information that both adheres to regulatory requirements and reflects the most current and comprehensive evidence base on vaccination in pregnancy.

1.1. Study objective

Our objective was to develop revised language statements for the use in pregnancy section of product labelling information that were clear, concise, and accurately interpreted by HCPs.

2. Material and methods

2.1. Study design

An emergent study design facilitated the flexibility that all consensus methods require [35,36]. We combined three consensus-based approaches to engage the strengths and minimize the limitations of each [39]: a Nominal Group Technique (NGT) meeting (Stage 1), a modified Delphi survey (Stage 2), and a consensus workshop (Stage 3). In NGT, participants meet directly, record ideas independently, and share their responses in a small group [40,41]. Delphi technique involves participants recording confidential responses to a problem via surveys [38,39,42]. A consensus workshop includes structured small-group working sessions, large-group sessions, and leaders sharing results throughout [43]. The three stages were conducted from December 2017 to April 2018 (Table 1).

2.2. Study participants

We purposefully sampled participants for each stage from different professions, Canadian regions, and career stages. We aimed to recruit public health experts, regulators, experts in vaccine

[2] In this article, we use the term "women" to refer to the majority of people who are vaccinated during pregnancy, maintain consistency with existing literature, and acknowledge the relevance of gender to end users' interpretations of pharmaceutical information [24,25]. It is not intended to suggest exclusion of pregnant individuals who do not identify as women from future research on this topic.

Table 1
Process and Data Collected in Stages 1–3.

Stage/Phase	Description
Stage 1: Nominal Group Technique Meeting Minutes (N = 14)[a]	Process: Drafted generic vaccine product monographs for use in the Delphi Technique Survey. Data: Meeting minutes from Dec 14, 2017 when stakeholders met in Halifax, Nova Scotia.
Stage 2: Delphi Technique Survey Data (N = 41)[b]	Process: Survey of stakeholders from across Canada in Feb-Mar 2018. Data: Responses to close-ended questions about preferred generic vaccine product monograph statements and open-ended questions about the extent to which the PM statements address safety and effectiveness.
Stage 3: Consensus Workshop Meeting Transcripts (N = 27)[b]	Process: Stakeholders met in Ottawa on March 27–28, 2018. Stakeholders revised existing product monograph statements and discussed the evidence, regulation, and language used in vaccine product monographs. Data: Transcripts from a two-day workshop with a sub-sample of Delphi survey respondents. Exit survey about the consensus process. Member check emailed feedback about the product label information statements.

[a] Stage 1 participants: healthcare providers, current or former members of the Canadian National Advisory Committee on Immunization (NACI), experts from public health, communication, law, vaccine evaluation, and social sciences
[b] Stage 2–3 participants: healthcare providers, regulators, industry representatives, current and former members of NACI, and experts from public health, communication, law, ethics, vaccine evaluation, and social sciences.

evaluation, current and former NACI members, social scientists, communication experts, legal experts, ethicists, immunization program managers, industry representatives, maternal HCPs, and public health nurses.

We recruited 14 participants for Stage 1 through the authors' professional networks, the Canadian Immunization Research Network, and the Society of Obstetricians and Gynaecologists of Canada. For Stage 2 (survey), we recruited participants through NGT participants' professional networks, the Society of Obstetricians and Gynaecologists of Canada, and the College of Family Physicians of Canada. We invited NGT participants (Stage 1) to complete the Delphi survey (Stage 2), along with 53 additional stakeholders. We then invited Delphi survey participants to the face-to-face consensus workshop (Stage 3). The diversity of stakeholders differed slightly in each stage (Table 1).

2.3. Study procedures

In Stage 1, project leaders presented the research problem and draft product label statements for hypothetical vaccines to NGT participants. These statements represented various levels of evidence of safety and effectiveness for vaccine use in pregnancy. Participants discussed the strengths and limitations of the proposed statements and revised them. We estimated consensus by having participants state support, objections, or suggest revisions to the statements.

In Stage 2, participants completed one round of a Delphi survey, which was modified for qualitative data analysis and integration with the other consensus methods [36,37]. The survey was developed by the investigators based on the NGT meeting discussions, pilot tested among three stakeholders not involved in the NGT, and subsequently distributed in English via email using Opinio survey software on a server hosted in Halifax, NS.

The survey included 20 close-ended and 21 open-ended questions capturing information on demographics, interpretation of product label statements, and two visual aids (Supplemental Content 1). The survey included example statements for five hypothetical vaccines (vaccines A to E) with different levels of evidence supporting their safety and effectiveness in pregnancy. We used hypothetical vaccines and diseases to avoid biasing responses by how HCPs may perceive the risks of influenza versus pertussis in women and infants. After reading the statements, participants were asked to rate how safe and effective they thought each vaccine was on a five-point scale, whether they would recommend the vaccine, and what changes they would suggest to the wording. Results from the survey were used to revise statements for each of vaccines A-E and develop three visual aids to initiate discussion during Stage 3.

Stage 3 engaged survey respondents who were available to attend the two-day workshop. The workshop included presentations on social, ethical, and legal issues surrounding product labels, and the Delphi survey results, as well as large group discussions and two breakout group sessions. Project leaders and researchers acted as moderators and note-takers for one French-speaking and three English-speaking breakout groups, and the large group discussions.

On day one, breakout groups of five to eight participants revised statements for *Vaccine A* and *Vaccine E* (Supplemental Content 2). After the first day, we modified our approach based on participant concerns about the applicability of the hypothetical vaccine statements to NRA requirements. On day two, the same breakout groups revised existing IIV and Tdap vaccine product label statements from the "use in pregnancy" section. The small groups reported their suggestions and concerns for the large group to discuss. Qualitative data were collected including meeting notes and transcriptions of audio-recorded large group and breakout group discussions.

Workshop participants completed an exit survey that included six Likert scale questions and open-ended questions about their perception of the consensus process. We prepared final product label statements after the meeting and circulated them to workshop participants via email for their feedback as a member check.

2.4. Ethics

The IWK Health Centre Research Ethics Board approved the research protocol (Project #1023139).

2.5. Data analysis

We measured consensus in Stages 2 and 3 using a spectrum ranging from very strong consensus (A) to dissensus (F) (Supplemental Content 3). We collected qualitative data from the three consensus stages to analyse for consensus on improving the language statements based on the types of feedback participants expressed (e.g., supportive statements, grammatical corrections, major revisions). Where the quantitative and qualitative criteria gave different ratings for consensus of a particular item, we applied the lower rating.

In Stage 2 (Delphi survey), we analysed quantitative data using descriptive statistics. We used SAS v 9.4 (SAS Institute, Cary, NC) to conduct cross-tabular analyses comparing participant responses to product label statements by demographic characteristics (e.g., region, profession, career stage). Two researchers coded open-ended responses in MS Excel for emergent themes, language ideas, and consensus. Project leaders reviewed the codes and interpretation.

In Stage 3, we coded transcripts and notes from the meeting using a content analysis approach to identify themes, language

ideas, and evidence of consensus. We utilized qualitative and quantitative criteria to measure consensus in the exit survey (e.g., thematic analysis to evaluate participants' perceptions of the consensus process; Likert scale means and percentage of positive responses on the Exit Survey).

3. Results

3.1. Stage 1 (nominal group technique)

The NGT meeting involved the study co-authors who are experts in public health, social science, law, obstetrics, infectious diseases, vaccinology, and epidemiology. Participants (N = 14) agreed with the study goals, revised hypothetical vaccine product label statements, and created visual representations of the vaccine product information to consider for inclusion in the package insert. We combined the revised statements into five product information statements and two visual aids for hypothetical vaccines to test in the Delphi survey (Supplemental Content 1).

3.2. Delphi survey

Forty-one of 62 (66%) invited stakeholders completed the survey. Respondents represented diverse areas of expertise from seven of the ten Canadian provinces, but none of the territories (Table 2). Respondents had a median of 20 years of experience in their role. Participant responses to the language statements are shown in Table 3. Participants' interpretations of vaccine safety and effectiveness varied according to the quality of evidence supporting each statement about vaccine safety or effectiveness. For example, stakeholders responded positively to *Vaccine C*, which had strong evidence of safety and effectiveness in pregnancy. However, substantial revisions were recommended for vaccines with known or theoretical risks (*Vaccine D*), no evidence for safety or effectiveness (*Vaccine E*), and moderate to limited quality evidence supporting safety or effectiveness (*Vaccine A* and *B*). HCPs were less likely to recommend vaccines with limited evidence to their patients even if recommended by the NITAG.

We identified common themes from participant comments. First, participants requested that terminology, such as "limited" or "moderate quality evidence," be clarified for consistent interpretation among the public, HCPs, and regulatory experts. Second, participants called for the removal of redundant information. Third, participants said that the tone of the language should align with the level of evidence and avoid subjective statements (e.g., *may* be safe versus *is* safe). Fourth, participants wanted additional information included in the statements such as NITAG recommendations, and evidence from observational studies and clinical trials not conducted by the manufacturer. Finally, comments by HCPs raised emergent themes, with some HCPs expressing trust in NACI recommendations regardless of the level of evidence for use, while others would only use vaccines with limited or no evidence if the risk of disease was high. Qualitative comments about whether to include the visual aids and how to improve them demonstrated extensive disagreement (rating between "D" and "F" on the consensus spectrum).

Based on the survey responses, we added details and lengthened statements to make vaccines *A*, *B*, *C*, *D*, and *E* less abstract, and changed the format (Supplemental Content 2).

3.3. Consensus workshop

Twenty-seven of 41 (59%) stakeholders who completed the Delphi survey attended the consensus workshop (Table 2). Early in the workshop, participants learned (most for the first time) that vaccine product labels are not intended to inform clinicians about recommendations for use. Many participants expressed concerns about this, leading to lengthy discussions of the purpose, regulation, and evidence-base of vaccine product labels in Canada. For example, a clinician noted that: "one of the things that has become clear... during our conversation is how big the gulf is between what the insert and monograph is for and what clinicians think it is for...." Another voiced concern about the regulation of vaccine product labels: "as of today, there is no regulator that consistently asks manufacturers to include effectiveness data, because there is no requisition that real life data post-marketing gets included." These discussions had implications for the language statements we developed. As Health Canada, like many NRAs, does not require regular updates to vaccine product information, participants suggested including the date of last update of the pregnancy subsection in the product label. Participants also developed a disclaimer for vaccine package inserts that explains their purpose in relation to NITAG recommendations (Table 4). Based on informal measures of consensus, we approached unanimity on the disclaimer statement.

Following these discussions, participants discussed the content, format, and language that the product label should contain and revised statements for IIV and Tdap vaccines. We did not attain group-wide consensus for *Vaccine A*, *Vaccine E*, or the visual aids. Revisions participants made to IIV and Tdap statements included shortening the pre-clinical data, expanding on recent post-marketing surveillance and observational data, and adding the NACI recommendation and a statement about the disease being

Table 2
Demographic Characteristics of Delphi Survey and Consensus Workshop Participants. (N = 41).

Participant characteristics	Delphi Survey (N = 41)	Consensus Workshop (N = 27)
	n (%)	**n (%)**
Region of practice		
Western Canada (Alberta, British Columbia, Manitoba)	10 (24)	7 (26)
Maritime Provinces (New Brunswick, Nova Scotia)	10 (24)	7 (26)
Ontario	14 (34)	8 (30)
Quebec	7 (17)	4 (15)
Outside Canada	0 (0)	1 (4)
Areas of expertise		
Maternal healthcare provider[a]	14 (34)	6 (22)
Clinical public health and infectious diseases[b]	11 (27)	10 (37)
Social sciences, law, and ethics[c]	7 (17)	5 (19)
Non-clinical public health and infectious diseases[d]	5 (12)	3 (11)
Representatives from industry[e]	4 (10)	3 (11)
Experience on NACI	N/A[f]	5 (19)
Years in practice		
3–10 years	10 (24)	N/A
11–20 years	13 (32)	N/A
21–40 years	18 (44)	N/A

N/A, not available.
[a] Includes midwives, obstetricians, family physicians, obstetrical/prenatal nurses, reproductive infectious diseases specialists, and obstetric internal medicine practitioners.
[b] Includes public health nurses, public health physicians, pediatric infectious diseases specialists, infectious diseases and infection prevention specialists, and pharmacists.
[c] Includes legal/law experts, social scientists, bioethicists, communication experts, and journalists.
[d] Includes epidemiologists, government regulators, and human factors engineers.
[e] Includes representatives from the pharmaceutical industry and medical affairs.
[f] We did not ask about NACI experience (current or former NACI member, liaison representative or ex-offico representative) on the Delphi Survey.

Table 3
Delphi Survey Responses.

Effectiveness Statement for Vaccines A-E (N = 41) **Do you think that giving Vaccine "X" to a pregnant woman will benefit the pregnant woman and her infant/ fetus?**	Yes n (%)	No n (%)	Neutral n (%)	Don't know n (%)
Vaccine C is effective in preventing disease in pregnant women and/or their infants/fetuses; **strong quality evidence**.	37 (90)	0 (0)	2 (5)	2 (5)
Vaccine A is effective in preventing disease in pregnant women and/or their infants/fetuses; **moderate quality evidence**.	29 (70)	0 (0)	9 (22)	3 (7)
Vaccine B: Current evidence suggests that Vaccine B is effective in preventing disease in pregnant women and/or their infants/fetuses; **limited quality evidence**.	13 (32)	3 (7)	13 (32)	12 (29)
Vaccine D: Effectiveness data… are not available for pregnant women or their fetuses/infants; **no evidence**. Vaccine D is effective in nonpregnant populations; **strong quality evidence.**	3 (7)	13 (32)	9 (22)	16 (39)
Vaccine E: Effectiveness data for this or similar vaccine products are not available for pregnant women or their fetuses/infants; **no evidence.** … Vaccine E is effective in nonpregnant populations; **limited quality evidence**.	0 (0)	15 (37)	7 (17)	19 (46)
Risk statement for Vaccines A-E (N = 41)				
Do you think that giving Vaccine "X" to a pregnant woman is safe for the pregnant woman and her infant/ fetus?	Yes	No	Neutral	Don't know
Vaccine C is safe for pregnant women and their infants/fetuses with no evidence of serious risks; **strong quality evidence**.	41 (1 0 0)	0 (0)	0 (0)	0 (0)
Vaccine A: Current evidence suggests that Vaccine A is safe (no serious risks) for pregnant women and their infants/fetuses; **limited evidence**.	12 (29)	4 (10)	13 (32)	12 (29)
Vaccine B: Safety data … are not available for pregnant women and their fetuses/infants; **no evidence**. Vaccine B is safe in nonpregnant populations; **strong quality evidence**. Studies in pregnant animal models identified an increased risk of fetal growth restriction… Consider use when the risk of severe disease is high in the mother and/or fetus.	1 (2)	16 (39)	4 (10)	20 (49)
Vaccine D: Current evidence suggests that there is a small increased risk of chorioamnionitis; **limited quality evidence**… Consider use when the risk of severe disease is high for the pregnant woman, fetus, or infant.	4 (10)	2 (5)	9 (22)	26 (63)
Vaccine E: Safety data … are not available for pregnant women or their infants/fetuses; **no evidence**. … Vaccine E is safe (no serious risks) in nonpregnant populations; **limited quality evidence**. Consider use when the risk of severe disease is high for the pregnant woman, fetus, or infant.	1 (2)	13 (32)	8 (20)	19 (46)
HCPs' recommendation in pregnancy for Vaccines A-E (N = 25)				
Would you recommend Vaccine X to your pregnant patients if it was recommended by national or provincial immunization advisory committees?	Yes	No	Don't Know	
Vaccine C	23 (96)	0 (0)	1 (4)	
Vaccine A	19 (79)	0 (0)	5 (21)	
Vaccine B	10 (42)	6 (25)	8 (33)	
Vaccine D	10 (42)	4 (17)	10 (42)	
Vaccine E	6 (25)	5 (21)	13 (54)	

prevented. Finally, participants organized vaccine product labels under subject headings and used gender-neutral language (Table 4). We achieved strong consensus (rating "B" on the consensus spectrum) on each section of the statements including: a statement that use in pregnancy is not contraindicated, NITAG recommendations, clinical considerations, effectiveness, safety, and the date the use in pregnancy section was updated. We achieved satisfactory consensus on the order of the statements describing vaccine safety and effectiveness (rating "C" on the consensus spectrum), and satisfactory to strong consensus on the use of the term effectiveness over efficacy (rating between "C" and "B" on the consensus spectrum).

3.4. Exit survey

Twenty-three of 27 participants (85%) completed the exit survey (Table 5). Participants expressed high levels of satisfaction with the opportunities to provide input, workshop facilitation, and workshop duration. The majority were satisfied with the workshop outcomes but only 48% felt the goals were achievable.

The uncertainties that emerged about the content and purpose of vaccine product label information were reflected in participants' comments on the exit survey, particularly among those who expressed lower satisfaction with the meeting outcomes and goals. One participant conveyed frustration with Health Canada's regulatory process for approving product labels: "[Very] difficult to [hear] … that what we identified as important would not happen." Another explained, "I wish the participants developed a better understanding of the purpose of [product labels], as opposed to [the] NACI recommendation." Participants' concerns about the purpose, regulation, and evidence used in vaccine product label statements exposed problems beyond the language used in those statements.

3.5. Member check

Following the workshop, three revised product label statements (IIV, Tdap, and a generic template) and the disclaimer were emailed to participants. Thirteen (48%) provided feedback. Participant comments demonstrated strong to very strong consensus on the revised IIV and Tdap statements (rating "A-" and "B+" respectively) (Supplemental Content 4). We achieved satisfactory consensus on the template product label statement (rating "C" on the consensus spectrum). Consensus on the product label disclaimer statement about the purpose and limitations of a vaccine product label was strong (rating "B" on the consensus spectrum). However, one participant rewrote that statement and voiced uncertainty about the purpose of the disclaimer. We integrated some of those changes into the final statement.

4. Discussion

The three stages of our consensus approach used emergent methods that were essential to achieving strong consensus on

Table 4
Revised PM Language Statements.

	Disclaimer Statement Intended for the Cover of Vaccine Product Label Information THIS DOCUMENT PRIMARILY CONTAINS PRODUCT-SPECIFIC information PROVIDED BY THE MANUFACTURER and approved by Health Canada. For independent evidence-informed advice for prescribing vaccines in humans, consult the National Advisory Committee on Immunization or provincial/territorial recommendations. [insert includes a website link to NACI statement]
Current IIV Product Label [48]	**Revised IIV Statement**
"Pregnancy Category B: A developmental and reproductive toxicity study has been performed in female rabbits at a dose approximately 20 times the human dose (on a mg/kg basis) and has revealed no evidence of impaired female fertility or harm to the fetus due to [the vaccine]. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, [the vaccine] should be given to a pregnant woman only if clearly needed. In the developmental and reproductive toxicity study, female rabbits were administered [the vaccine] or control saline (each 0.5 mL/dose) by intramuscular injection 24 and 10 days before insemination, and on Days 6, 12, and 27 of gestation. The administration of [the vaccine] did not result in systemic maternal toxicity (no adverse clinical signs and no change in body weight or food consumption). In addition, no adverse effects on pregnancy, parturition."	**Special Populations** Unless explicitly stated below, *Vaccine-A* is not contraindicated for the populations in this section. **Use in Pregnancy:** NACI recommends influenza vaccination in pregnancy, see: [monograph includes a website link] **Clinical considerations**: Influenza increases the risk of severe illness and adverse outcomes during pregnancy. Influenza is associated with severe disease in infants. **Effectiveness**: Vaccination against influenza during pregnancy protects the pregnant person and the infant up to six months of age against severe disease (based on post-marketing surveillance by *Manufacturer-X* with similar inactivated influenza vaccines).The effectiveness of *Vaccine-A* when administered in pregnancy has not yet been evaluated in adequate and well-controlled studies by *Manufacturer-X*. **Safety**: No vaccine related serious adverse pregnancy, fetal, or neonatal outcomes have been observed when inactivated *Vaccine-A* vaccines are administered in the second and third trimesters of pregnancy (based on post-marketing surveillance). Few studies have assessed the safety of first trimester vaccination. The safety of *Vaccine-A* when administered in pregnancy has not yet been evaluated in adequate and well-controlled studies by *Manufacturer-X*. No direct or indirect adverse reproductive or developmental effects have been observed in animal studies with *Vaccine-A* by *Manufacturer-X*. This information is accurate as of 15 May 2017.
Current Tdap Product Label [49]	**Revised Tdap Statement**
"Pregnant Women: Safety data from a prospective observational study where [the vaccine] was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from post-marketing surveillance where pregnant women were exposed to [the vaccine] have shown no vaccine related adverse effect on pregnancy or on the health of the fetus/newborn child. The use of [the vaccine] may be considered during the third trimester of pregnancy. Human data from prospective clinical studies on the use of [the vaccine] during the first and second trimester of pregnancy are not available. Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with [the vaccine] during pregnancy. The clinical relevance of this observation is unknown. Animal studies with [the vaccine] do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/fetal development, parturition or post-natal development (see TOXICOLOGY). [The vaccine] should only be used during pregnancy when the possible advantages outweigh the possible risks for the fetus."	**Special Populations:** Unless explicitly stated below, *Vaccine-C* is not contraindicated for the populations in this section. **Use in Pregnancy:** NACI recommends pertussis vaccination in every pregnancy, see: [monograph includes a website link] **Clinical considerations**: Pertussis is associated with severe disease in infants. **Effectiveness:** *Vaccine-C* is 90% effective for protection of the infant against severe pertussis, based on prospective surveillance, case-control, and cohort studies. The *Manufacturer-Y* has limited data to indicate that pertussis vaccination of a pregnant person produces antibodies that may reduce the magnitude of the immune response to other vaccines in the infant. The clinical relevance of this observation is unknown at this time. **Safety**: No vaccine related serious adverse pregnancy, fetal, or neonatal outcomes have been observed when pertussis is used in the [second and third] trimesters of pregnancy, based on a prospective observational study by *Manufacturer-Y* with this vaccine. Few studies have assessed the safety of first trimester vaccination. This information is accurate as of 14 Apr 2016.

revised vaccine product label statements for IIV and Tdap. The Delphi and exit surveys stimulated stakeholder reflection on the statements and allowed for anonymous feedback [39,40]. The NGT meeting and consensus workshop enabled participants to see real-time results, encouraged learning/sharing, and granted flexibility to explore stakeholders' concerns [39]. These discussions uncovered how participants' understandings of the purpose, content, and evidence used in vaccine product information differed from its regulatory purpose and requirements.

The multi-stage consensus process with diverse stakeholders involved in vaccine manufacturing, regulation, developing vaccine recommendations, immunization program delivery and evaluation, vaccine administration, and communication, identified different views of the regulatory intention and clinical use of vaccine product label information. NRA representatives agreed on the restrictions on product information content and purpose while vaccine manufacturers were open to changes that fell within NRA guidelines. All other stakeholders, regardless of area of expertise or experience with NACI, had a very different perception. Many HCPs were unaware of the NRA's stated purpose of vaccine product information, yet, HCPs often base their clinical decisions on product label information [27,28]. HCPs noted that patients may use that information to inform decisions about vaccination, and vaccine hesitant members of the public post their concerns using cautionary product label statements online. In this study, HCPs argued that product information content should change to include recommendations for use and post-market clinical and epidemiological evidence.

Despite this unexpected finding, we achieved consensus among stakeholders on the revised evidence-based statements for the "use in pregnancy" section in vaccine product information for IIV and Tdap, and on a disclaimer statement for the cover of vaccine package inserts. The disclaimer clarifies the purpose, evidence, limitations of the product label, and explicitly refers the reader to the NITAG statement for information on vaccine use in pregnancy. The format of the statements could be adapted to other vaccine products recommended for use in pregnancy in other countries. Incorporating the revised product information and disclaimer statements into product label information is expected to improve consistency in interpretation by HCPs and support evidence-informed vaccine use in pregnancy.

Efforts have been made in other countries to resolve inconsistencies between NITAG recommendations and product information, and to develop clearer language for product information

Table 5
Exit Survey Summary.

5-point Likert Scale Feedback (N = 23)				
Opportunities to provide input, meeting facilitation, and time				
*How satisfied are you with the opportunities for you to provide input during the **large group** meetings?*	**Unsatisfied (1–2)** n (%)	**Neutral (3)** n (%)	**Satisfied (4–5)** n (%)	**Consensus Rating (Mean)**
	1 (4)	2 (9)	20 (87)	A (4.4)
*How satisfied are you with the opportunities for you to provide input during the **breakout groups** (small group meetings)?*	**Unsatisfied (1–2)**	**Neutral (3)**	**Satisfied (4–5)**	**Consensus Rating (Mean)**
	0 (0)	1 (4)	22 (96)	A (4.8)
How effective was/were the small group leader(s) in keeping the discussion on track and helping the group to achieve its goals?	**Ineffective (1–2)**	**Neutral (3)**	**Effective (4–5)**	**Consensus Rating (Mean)**
	2 (9)	2 (9)	19 (83)	A- (4.3)
How adequate was the time allotted for this meeting?	**Inadequate (1–2)**	**Neutral (3)**	**Adequate (4–5)**	**Consensus Rating (Mean)**
	1 (4)	3 (13)	18 (78)	B (4.0)
Achievability of the meeting goals and satisfaction with meeting outcomes				
How satisfied are you with the outcomes of our meeting?	**Unsatisfied (1–2)**	**Neutral (3)**	**Satisfied (4–5)**	**Consensus Rating (Mean)**
	2 (9)	6 (26)	15 (65)	C (3.7)
How achievable were our consensus workshop goals?	**Impossible (1–2)**	**Neutral (3)**	**Achievable (4–5)**	**Consensus Rating (Mean)**
	6 (26)	6 (26)	11 (48)	D (3.2)
Open-Ended Comments (N = 11[a])				**N = 11**
Positive comments about the meeting or project				7 (63)
Frustration with vaccine product label regulation, purpose, or evidence-base				7 (63)
Recommendation for what may have improved the meeting				5 (46)
There is more work to do beyond the consensus workshop				2 (18)

[a] The total per theme is greater than 11 because many respondents wrote comments that fit with two or more themes.

statements [28,29]. For example, the FDA has developed the "Pregnancy Drug and Lactation Labelling Rule," which includes the replacement of the lettered risk categories with a narrative summary of available information about pharmaceutical product use during pregnancy [33]. The WHO developed guidelines to facilitate interpretation of information in IIV package inserts and use of IIV in maternal immunization programs [31]. The WHO, several NITAGs, and NRAs are working with vaccine manufacturers to develop guidelines to modify vaccine product language requirements for descriptions of the evidence for the safety, efficacy, and effectiveness of vaccines in pregnancy [29,33,44]. Product information content and regulation for the same pharmaceutical products differ between countries [6,45]. To our knowledge, this is the first study to use emergent consensus-based methods that enable the exploration of unanticipated concerns from diverse stakeholders to improve product label information. Our process involved a diversity of expertise including frontline HCPs who use product information to inform clinical decisions. Our results suggest that it is imperative to include HCPs in the development, revision, or review of vaccine product information.

Our study shows that there is further need to evaluate the purpose, regulation, and evidence-based use of vaccine product information. Additional revisions to product information may call for changes to regulatory requirements governing their format, content, and evidence. Participant recommendations that NRAs mandate regular updates, support research into vaccine use during pregnancy, and add a hyperlink to NITAG recommendations are consistent with previous research [28]. NRAs might collect, monitor, and evaluate the safety and effectiveness of post-market non-clinical trial data to better describe product use in specific populations (e.g., pregnant persons, or patients with immune deficiencies) [32]. In fact, some NRAs (e.g., European Medicines Agency) encourage the inclusion of observational data in vaccine product label information [46] [Kari Johansson, Hanna Nohyek. Personal Communications [in-person and email] to NE MacDonald 2019].

4.1. Limitations

Although we intended to measure consensus at the workshop through anonymous ranking and discussion, time constraints resulting from the extent and complexity of the discussion necessitated focus on qualitative measures of consensus. Limited opportunities for anonymous feedback could have prevented participants with contrary views from having their opinions voiced or considered more fully. However, workshop transcripts demonstrated consensus for the revised statements and anonymous exit survey responses showed high satisfaction with opportunities to provide feedback. Participants were purposefully sampled and their views may not be generalizable to others in their profession or region. In particular, we were unsuccessful in recruiting participants from indigenous communities and Northern Canada. We intentionally excluded non-experts in the wider public, as it was beyond the scope of the project. To ensure the product label statements are consistently interpreted by HCPs, we are evaluating them in a survey of Canadian HCPs. Translation of the statements into other languages and their evaluation in other contexts is needed to ensure consistency in their interpretation.

4.2. Conclusion

We used an innovative approach to achieve consensus on revised vaccine product label statements and identified divergent understandings of the purpose, content, and evidence used in product information. This preliminary finding requires further research and may suggest the need to educate healthcare providers about the purpose of the product label and the regulation process. The proposed revised statements have clear, gender-neutral lan-

guage, are consistently structured, and include data from post-marketing surveillance and observational studies. Because it is impossible to predict what unique problems could influence how end users interpret label information for other vaccine and drug products, consensus-based approaches and consultation with end users should be applied routinely in the review of vaccine product information and similar regulatory documents to ensure that all stakeholders interpret the information similarly. Given growing concerns about fake news and science deniers in health [47], it is imperative that NRA-approved statements on the product label not contradict or undermine public health recommendations based on more recent evidence.

5. Data statement

Transcripts and survey data used in this project are confidential. Supplemental materials include summaries of that data and the Delphi survey used in this study.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Karina A Top has received grants from GSK and consultancy fees from Pfizer outside the submitted work. All other authors report no conflicts of interest.].

Acknowledgements

The authors gratefully acknowledge the expert technical assistance of Poh Chua (Dalhousie), Lingyun Ye, Kelly Lefurgey (Canadian Center for Vaccinology), and Kirsten Weagle (Dalhousie). The authors thank the Society of Obstetricians and Gynaecologists of Canada for assistance with study logistics and coordination, especially Dr. Jocelyn Cook and Kyla Kaminsky.

Funding

This project was funded by the Public Health Agency of Canada, in collaboration with the Society of Obstetricians and Gynaecologists of Canada.

Disclosures

KAT has received grants from GSK and consultancy fees from Pfizer outside the submitted work. All other authors report no conflicts of interest. All authors have approved the final version of this article. All authors attest they meet the ICMJE criteria for authorship.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.063.

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