Do health care providers trust product monograph information regarding use of vaccines in pregnancy? A qualitative study

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Abstract

Background: Influenza immunization is recommended in pregnancy to prevent severe infections in pregnant women and newborns, yet vaccine uptake remains low. Studies suggest that cautionary language in vaccine product monographs regarding safety and use in pregnancy affects health care providers' perceptions of vaccine safety and how they counsel pregnant women.

Objective: To conduct a qualitative analysis of health care provider perceptions of the safety of inactivated influenza vaccines and their recommendations for use in pregnancy based on product monograph language statements.

Methods: Health care providers were recruited at two international health conferences and from teaching programs in Ethiopia, Ghana, Uganda, and Laos during September and October 2015. After reading the product monograph excerpts for three licensed inactivated influenza vaccines, participants completed a ten-item online survey with quantitative and qualitative components that captured perceptions of vaccine safety.

Results: Health care providers identified a lack of trust in manufacturers' and product monograph information. They perceived product monograph language as ambiguous and not "up-to-date" with current evidence. Health care providers wanted product monograph language that clearly conveyed evidence for the risks and benefits of the vaccine in an understandable manner.

Conclusion: This study suggests that adopting best practices in the wording of product monographs would help to support evidence-based use of vaccines in pregnant women.

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Introduction

Seasonal influenza is associated with an increased risk of hospitalization during pregnancy and in infants younger than six months of age (1,2). The Canadian National Advisory Committee on Immunization (NACI) and World Health Organization (WHO) recommend influenza immunization during pregnancy to reduce the risk of severe infection in pregnancy and early infancy (1,3). The safety of influenza immunization in pregnancy has been demonstrated in numerous studies and summarized in several systematic reviews (3-6). Based on systematic reviews, including a review by the WHO Global Advisory Committee on Vaccine Safety (3), inactivated influenza vaccines (IIVs) demonstrated no increased risk of adverse outcomes, such as spontaneous abortion, stillbirth or congenital anomalies. Yet vaccine uptake among pregnant women remains low (7,8). Unresolved safety concerns among health care providers and patients pose a potential barrier to vaccine acceptance.

The NACI, Canada's National Immunization Technical Advisory Group (NITAG), reviews evidence from clinical trials and observational studies of the safety and effectiveness of vaccines licensed for use in Canada, as well as the epidemiology of the disease, and develops recommendations for vaccine use (1). Influenza vaccination recommendations updated after annual review of the most recent data are freely accessible online in full and as a pocket guide (1).

Vaccine product monographs are another source of vaccine information for health care providers, presenting information about approved indications, contraindications, warnings and precautions. Publicly available online, product monographs are meant to be "used by health care professionals in making prescribing decisions and in counselling patients about a product's risks and benefits" (9). The product monograph text

is developed by the vaccine manufacturers with input and authorization from Health Canada, the National Regulatory Authority (NRA). Health Canada reviews safety and effectiveness data presented by the manufacturer that is generally limited to product-specific data from randomized clinical trials; however, few clinical trials on IIVs have been conducted in pregnant women (6). Consequently, product monograph language may appear more cautionary than NACI recommendations (e.g., "use only following the advice of a health care professional, based on consideration of the benefits and risks to the mother and the foetus", FluLaval®, GlaxoSmithKline, Sainte-Foy, Québec) (10). The above statement also highlights the circularity of the language, which directs the reader (a health care professional) to follow the advice of a health care professional. Moreover, product monograph language may differ markedly among vaccines with similar composition and safety profiles (11). These factors may contribute to confusion among health care providers.

We conducted a survey with quantitative and qualitative components to determine the effects of product monograph language statements on health care providers' perceptions of the safety of IIVs and their recommendations for use in pregnancy (12). The 141 survey respondents included obstetricians, family physicians, nurses, midwives, and other health professionals from 49 low-, middle- and high-income countries, including Canada, and representing the six WHO regions.

The quantitative results, published elsewhere, demonstrated that health care providers in low-, middle- and high-income countries perceived the safety of the vaccine differently, depending on which of three product monograph statements they read, with fewer than half rating the vaccine as safe (12). Many respondents provided additional comments regarding product monograph language. We conducted a qualitative analysis of those comments to identify themes and suggestions for improving product monograph language.

Methods

Study design and subjects

Health professionals who provided prenatal care were eligible to complete a survey regarding their perceptions of product monograph statements describing influenza vaccine safety and use in pregnancy. Between September and October 2015, participants were recruited at two health conferences: International Federation of Gynaecology and Obstetrics, Vancouver; and Global Maternal Newborn Health Conference, Mexico City. To include representation from all six WHO regions, participants were recruited from teaching programs for local health care providers in Ethiopia, Ghana, Uganda and Laos (12). To ensure a diverse sample of respondents, a maximum of six participants could be enrolled from the same country. In order to gather data specific to the Canadian context, we did not limit the number of Canadian respondents who could participate.

Survey instrument

The development of the 10-item survey instrument has been described previously (12). Briefly, respondents were asked to read three different statements from product monographs for similar vaccines (IIVs) with similar safety profiles that were licensed in the United States (US), Canada and France. All three vaccines were prequalified by the WHO for procurement by United Nations agencies. The first statement emphasized uncertainty: "safety and effectiveness in pregnancy is not established [and it should be used] only if clearly needed" (Fluvirin®, Novartis Vaccines and Diagnostics, Ltd, Liverpool, United Kingdom; Fluzone®, Sanofi Pasteur Inc, Swiftwater, Pennsylvania, US). The second statement described conditions for vaccine use: "use only following the advice of a health care professional, based on consideration of the benefits and risks to the mother and the foetus" (FluLaval®, GlaxoSmithKline, Sainte-Foy, Québec, Canada). The third statement most closely aligned with public health recommendations: "use only from the 2nd pregnancy trimester onwards [limiting use throughout pregnancy to women] at risk of complications of infection" (Vaxigrip®, Sanofi Pasteur Ltd, Lyon, France).

Respondents were then asked to indicate their perception of the safety of the vaccine described in the statement and provide additional comments about product monograph information regarding vaccine use in pregnancy. The final question was open-ended, seeking further comments regarding vaccine product monographs. The survey was professionally translated into French and Spanish, and back-translated.

Opinion survey software version 6.9.1 (ObjectPlanet, Oslo, Norway) was used on a server hosted in Halifax, Nova Scotia, Canada.

Analysis and synthesis

Four co-authors (CA, KAT, NEM and JEG) analysed free text responses qualitatively via inductive content analysis using established methodology to identify themes (13). One co-author (CA) then refined the themes over several subsequent iterations. The co-authors KAT, NEM and JEG reviewed and approved the final themes. Data were hand-coded.

Ethics

This study received ethics approval from the IWK Health Centre Research Ethics Board (Approval #1020057) and WHO Research Ethics Review Committee.

Results

Sixty-one respondents provided comments about product monograph information, of which eight (14%) comments were from Canadians and 44 (72%) comments were from respondents in low- and middle-income countries. Comments came from all WHO regions and broadly represented professions and languages.

The principal theme was lack of trust in product monograph content and vaccine manufacturers (**Table 1**). Respondents described product monograph statements as "ambiguous", non-specific and lacking essential information. Several respondents stated that product monographs are not "up-to-date" with current evidence. Some respondents expressed a view that product monograph content is restricted by

vaccine manufacturers who are "protecting themselves against litigation". Respondents indicated that they were more inclined to trust organizations such as the WHO for vaccine information and guidance, rather than the product monograph.

Table 1: Major themes identified from the open-ended question, "Do you have any specific comments to add about product monograph safety statements on vaccines that might be used in pregnancy?"

Themes	Examples
Lack of trust in product monograph content	"Statements are ambiguous and not helpful" – Obstetrician, Canada "Some product monographs confuse. Make me anxious about using in pregnant women even when recommended by the immunization program. Why does monograph says is risk when program recommends? Who is correct?" – Midwife, Ethiopia "Sometimes the monographs are not up to date with the current literature and therefore can be very misleading regarding effectiveness and safety" – Obstetrician, Canada "Instead of having a blanket statement, like 'it's not safe', it should be specific about trimesters/ side-effects so that you can properly weigh the benefits and the risks." – Midwife, Botswana "Monographs should be authenticated by professional expert[s] and meta-analysis" – Obstetrician, India "Should be user-friendly to read" – Obstetrician, Indonesia
Lack of trust in manufacturers	"Manufacturers are usually very reluctant in their advices [sic] for pregnant women, which can lead to more harm than good. Therefore I usually follow the authority guidelines in these." – Obstetrician, Netherlands "Since product monographs are written by pharmaceutical companies, that have an extra agenda of protecting themselves against litigation, it is my routine to consult other sources of information" – Obstetrician, Sweden
Lack of evidence regarding vaccine safety in pregnancy	"Vaccines need to be tested in pregnancy so [we] know [they are] safe" – Midwife, Ethiopia "It should be clear that the data comes from research studies…" – Obstetrician, Democratic Republic of Congo "Vaccines should be used in pregnancy only if they are not harmful to both mother and her baby." – Obstetrician, Nigeria

Respondents opined the lack of evidence of vaccine safety in pregnancy. They expressed low tolerance for risk and the need for certainty when caring for pregnant women. Some respondents stated that they would only feel comfortable administering a vaccine if safety could be assured. They called for more research into vaccine safety in pregnancy while acknowledging the difficulties associated with such investigation.

To improve the product monographs, some respondents called for more specific information regarding vaccine efficacy and the risks associated with use in pregnancy. Others indicated that product monographs ought to be "easy to read" and written in "laymen [sic] language".

Discussion

The results suggest that health care providers were distrustful of vaccine product monographs and manufacturers. This is concerning because our quantitative results showed that the majority of health care providers read product monographs at least occasionally or for new products (12).

The qualitative findings add to the quantitative findings which showed that health care providers' perceptions of the safety of the vaccine were affected by the language in the product monograph statements and that language affected their recommendations to patients about vaccination; for example, after reading the statement, "safety and effectiveness in pregnancy is not established [use] only if clearly needed", 38% of respondents perceived the vaccine described in the statement as moderately or very unsafe and 18% of respondents indicated that they would not recommend the vaccine if it was recommended by national public health authorities. In contrast, after reading the statement, "use only from the second pregnancy trimester onwards", 28% of respondents perceived the vaccine as unsafe and 12% would not recommend the vaccine. Approximately 75% of respondents indicated that the language would affect how they counselled patients about immunization during pregnancy (12).

We hypothesized that perceptions among health care providers that manufacturers restrict product monograph content and product monographs disagree with NACI recommendations contribute to distrust of product monograph information.

Respondents expressed a desire for more informative, clearly worded product monographs that provide guidance for vaccine use, suggesting that health care providers want product monographs to include detailed information about the safety and effectiveness of the vaccine in pregnancy. Comments by respondents that product monographs should be understandable to a layperson highlight the challenges of revising the product monographs.

Regulators and public health organizations, as well as the WHO Strategic Advisory Group of Experts on Immunization, are beginning to recognize that differences between product monographs and NITAG (e.g., NACI) recommendations may influence vaccine uptake, and have called on NRAs and NITAGs to resolve these differences (14,15). The WHO and several NRAs have developed guidance for interpreting the pregnancy subsections of the monograph and have begun to revise product monograph language (14,16). These efforts, however, have not involved end users (i.e., frontline health care providers).

With support from the Public Health Agency of Canada, in collaboration with the Society of Obstetricians and Gynaecologists of Canada, we have adopted an interdisciplinary approach to develop product monograph language that will help to convey the quality and specificity of the evidence regarding vaccine safety and effectiveness in pregnancy to health care providers, and thus promote evidence-based use of vaccines. This research directly involves health care providers, public health experts, epidemiologists, legal scholars, social scientists, Health Canada regulators and other key stakeholders. We expect that this work will inform efforts to standardize product monograph language for vaccines with similar safety profiles and levels of

evidence in Canada and abroad. This will be an important first step to improve the product monographs and increase trust among Canadian health care providers in vaccines recommended in pregnancy.

In addition, the findings suggest a need for Health Canada to work with manufacturers and independent evaluators to update and reconcile product monograph content with the most recent evidence. They may consider including a hyperlink to the NACI recommendation in the product monograph so readers can access the most up-to-date guidance for vaccine use. We also encourage Health Canada and NACI to participate in international efforts to resolve perceived conflicts between product monographs and public health recommendations. Health Canada may consider, along with other NRAs, the need to impose regular manufacturer updates. Finally, further research into vaccine safety and effectiveness in pregnancy and enhanced active surveillance for adverse events during pregnancy and the newborn period are needed to ensure that product monographs and NACI recommendations are supported by high quality evidence throughout the vaccine lifecycle.

This study had limitations. Convenience sampling may have resulted in selection and response bias. Participants recruited at the two conferences may not have been representative of frontline health care workers in Canada or other countries. Most comments were from respondents in low- and middle-income countries who may have different perspectives than Canadian health care providers; however, responses to the multiple-choice questions did not differ by country income level or WHO region (12).

Conclusions

Rather than enabling the evidence-based use of vaccines, ambiguously worded and outdated product monograph statements may be a barrier to vaccine uptake during pregnancy in Canada. Health Canada, NACI and vaccine manufacturers should consider adopting best practices for developing product monograph content that clearly conveys the risks and benefits of vaccination during pregnancy in language that health care providers can understand.

Authors' statement

KAT – Conceptualization, investigation, analysis, writing – original draft
CA – Investigation, analysis, writing – review and editing
JG – Analysis and interpretation, writing – review and editing
HS, JM, SAM – Investigation, writing – review and editing
NEM – Conceptualization, investigation, analysis, writing – review and editing

Conflict of interest

KAT has received research support and consultancy fees from Pfizer and research grants from GlaxoSmithKline outside the submitted work. SAM has received research grants from GlaxoSmithKline and Pfizer outside the submitted work. All other authors report no conflicts of interest.

Contributors

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