

COMMENTARY



Regulatory agencies have a role to play in maintaining consumer confidence in vaccine safety for pregnant women

Michelle L. Giles ^{a,b} and Allen C. Cheng^{c,d}

^aDepartment of Obstetrics and Gynaecology, Monash University, Melbourne, Australia; ^bInfectious Diseases Unit, Alfred Health, Melbourne, Australia; ^cCentral Clinical School, Monash University, Melbourne, Australia; ^dSchool of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

ARTICLE HISTORY Received 26 December 2019; Accepted 15 January 2020

In 2012, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization advised that pregnant women were the most important risk group to benefit from inactivated seasonal influenza vaccination.¹ Pregnant women have been identified as a priority group based on data suggesting they are at increased risk for severe morbidity and mortality, along with data suggesting that in addition to maternal benefits, there are benefits for the fetus and neonate.^{2–4}

A recent meta-analysis of four randomized controlled trials and three observational studies reported that maternal influenza vaccination reduced the risk of laboratory-confirmed influenza in infants less than 6 months of age by 48% (95% CI 33% to 59%).⁵

Despite recommendations for pregnant women to be vaccinated against influenza dating back to the 1960s,⁶ and increasingly professional organizations echoing the importance of this intervention, there has been slow progress in implementation in low and middle income countries.^{7,8} In addition, even in high-income settings where a nationally funded program exists, reported coverage remains low^{9–12} despite an increase in public awareness of influenza and its impact on pregnant women and neonates since 2009.

It is therefore important to understand the barriers and enablers to influenza vaccine uptake in pregnant women. Barriers and enablers to influenza vaccine uptake in pregnancy can be at an individual level (including pregnant women or health-care workers) or at a service delivery level (including issues related to access, cost, and policy). At a service delivery level, systems to facilitate efficient access to vaccine such as at the point of antenatal care can increase uptake significantly.¹³ At an individual level, however, health-care provider recommendation is consistently reported as the most important predictor of uptake.¹⁴ Many pregnant women also have concerns about vaccine safety, with many surveys suggesting that respondents believed that vaccines could cause harm to themselves or their fetus.¹⁴ In one Canadian study, 45% of respondents reported that they believed that vaccines were unsafe in pregnancy, and nearly 80% believed that the vaccine could cause birth defects.¹⁵

To address these concerns, it is important that publicly available information on vaccines in pregnancy for both health-care providers and consumers is evidence-based and

consistent. It has been speculated that an additional obstacle to recommendation by health-care providers and uptake by women relates to the language and content contained in the vaccine product information.¹⁶ Health-care providers and the public may find it confusing when reconciling policy recommendations and promotional information on immunization programs with the information contained in regulatory summaries for health-care professionals and consumers.

A published review of product information by Proveaux and colleagues reported on 96 separate vaccines and found that 20 of these (21%) included language suggesting that official recommendations should be “considered”, half of the products suggested users consult a health-care provider to determine whether the product should be given during pregnancy, 27% suggested use “if clearly needed” without defining what clearly needed meant and only 10 of 98 product information suggested use during pregnancy.¹⁷ Product information for four vaccines indicated that influenza vaccine should not be used in pregnant women. In addition, a subsequent study of 141 maternal health-care providers from 49 countries in all six WHO regions suggested that health-care providers perceive product information as contradicting WHO and national immunization recommendations and that this could affect their decision to recommend the vaccine to pregnant women.¹⁶ These authors also speculate that reproducing national or WHO recommendations for vaccine use during pregnancy in the product information, when aligned with the product’s safety profile, may help improve vaccine uptake in pregnancy.¹⁶

In 2015 the World Health Organization held a working group meeting on labeling information of influenza vaccines intended to be used in pregnant women.¹⁸ The purpose of this meeting was to explore the need for guidance to help the interpretation of the information in the pregnancy sections of influenza vaccine product information. It was recognized that a limiting factor to change was that in most countries the format and content of the product information is defined in law and approved by the national regulatory agency. In addition, in many countries, the system relies on the manufacturer to lead the initiative for change and provide supportive data. In addition, there is some controversy as to whether a “class approach” can be applied to all licensed.

Regulatory agencies have different approaches to assessing and communicating the risks of medicines and vaccines in pregnancy. For example, in Australia, a categorization system is used taking into account the known harmful effects of medicines on the developing baby, including the potential to cause birth defects, unwanted pharmacological effects around the time of birth and problems later in life (Table 1). The European Medicines Agency uses an integrated approach in risk assessment and recommendations for labeling are based on non-clinical and clinical data.¹⁹ In 2015, the pregnancy and lactation labeling rule (PLLR) was implemented by the US FDA.²⁰ This replaced a categorical system (risk categories A, B, C, D, and X) with a narrative summary of the risks of using a drug during pregnancy. These summaries are based on available human and/or animal data with an accompanying discussion of the data. In addition, when one influenza vaccine is available across different settings the differences in information included in product information (for the same product and target population) may lead to confusion. An example of this is demonstrated in Table 2.

In 2017, Australia had low maternal influenza vaccine coverage despite a fully funded national program. This prompted a reexamination of potential barriers to uptake, including the pregnancy risk categorization and narrative description of risk in the product information. Australia's medicines regulator, the

Table 1. Australian categorization system for prescribing medicines in pregnancy.

Category	Description
Category A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
Category B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage
Category B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
Category B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans
Category C	Drugs which owing to their pharmacological effects have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.
Category D	Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.
Category X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Table 2. Wording of pregnancy risk for one quadrivalent vaccine available in multiple settings (Sanofi quadrivalent influenza vaccine; FluQuadri and Fluzone Quadrivalent).

Setting	Excerpt from product information/summary of product characteristics
United States (FDA) ²²	All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data with Fluzone Quadrivalent use in pregnant women are insufficient to inform vaccine-associated risk of adverse developmental outcomes. Pregnant women are at increased risk of complications associated with influenza infection compared to non-pregnant women. Pregnant women who contract influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.
Australia (TGA) ²³	Data from studies involving large numbers of women (> 80,000) vaccinated during pregnancy with inactivated influenza vaccines do not indicate any adverse fetal and maternal outcomes attributable to the vaccine. FluQuadri should be given to a pregnant woman following an assessment of the risks and benefits. Because of the known adverse consequences of influenza infection in pregnant women, health authorities recommend vaccination of pregnant women.
Europe (EMC) ²⁴	Pregnant women are at high risk of influenza complications, including premature labor and delivery, hospitalization, and death: pregnant women should receive an influenza vaccine. Quadrivalent Influenza Vaccine (split virion, inactivated) can be used in all stages of pregnancy. Larger datasets on safety of inactivated influenza vaccines are available for the second and third trimesters, compared with the first trimester; however, data from worldwide use of inactivated influenza vaccines, including Inactivated Influenza Vaccine (Split Virion) BP (trivalent inactivated influenza vaccine), do not indicate any adverse fetal and maternal outcomes attributable to the vaccine. Data from four clinical studies with the trivalent inactivated influenza vaccine (Inactivated Influenza Vaccine (Split Virion) BP thiomersal-free formulation) administered in pregnant women during the second or third trimester (more than 5000 exposed pregnancies and more than 5000 live births followed up to approximately 6 months post-partum) did not indicate any adverse fetal, newborn, infant and maternal outcomes attributable to the vaccine. In clinical studies conducted in South Africa and Nepal, there were no significant differences between the Inactivated Influenza Vaccine (Split Virion) BP and placebo groups with regards to fetal, newborn, infant and maternal outcomes (including miscarriage, stillbirth, premature birth, low birth weight). In a study conducted in Mali, there were no significant differences between the Inactivated Influenza Vaccine (Split Virion) BP and control vaccine (quadrivalent meningococcal conjugate vaccine) groups with regards to prematurity rate, stillbirth rate and low birth weight/small for gestational age rate.

Therapeutic Goods Administration advised that a summary of the current evidence on the safety of vaccines would facilitate submissions from sponsors to amend the product information. The Department of Health commissioned a systematic review of pregnancy risks.²¹ This systematic review and other available spontaneous reporting data were reviewed and endorsed by Australian Technical Advisory Group on Immunization and the Advisory Committee for Vaccines. Several vaccine sponsors have subsequently successfully applied to change the categorization of their vaccine products and update the product information for influenza vaccines (Table 3).

Table 3. Product information of the three influenza vaccines available in Australia for pregnant women in 2017 and 2019.

	Influenza vaccines available in Australia (2017) extracts from product information	Influenza vaccines available in (2019) extracts from product information
Afluria Quad (Seqirus) QIIV Non-adjuncted	Use in pregnancy: Category B2 The safety and effectiveness of Afluria Quad™ vaccine has not been established in pregnant women. Therefore careful consideration should be made regarding the benefits and risks prior to administration of Afluria Quad™ vaccine to pregnant women who are pregnant or plan to become pregnant.	Use in pregnancy: Category A Influenza vaccination is recommended for pregnant women during any stage of pregnancy. This recommendation is based on the known adverse consequences of influenza infection during pregnancy and the large body of data showing that large numbers of women have been vaccinated during pregnancy with inactivated influenza vaccines with no increased risk of adverse fetal or maternal outcomes attributable to the vaccine. Afluria® Quad vaccine should be given to a pregnant woman following an assessment of the risks and benefits.
FluQuadri (Sanofi-Aventis) QIIV Non-adjuncted	Use in Pregnancy: Category B1 Data from worldwide use of inactivated influenza vaccines in pregnant women and experience of use of TIV in countries where inactivated influenza vaccines are recommended in all stages of pregnancy do not indicate any adverse fetal and maternal outcomes attributable to the vaccine. FluQuadri should be given to a pregnant woman following an assessment of the risks and benefits. Health authorities recommend vaccination of pregnant women.	Use in Pregnancy: Category A Data from studies involving large numbers of women (> 80,000) vaccinated during pregnancy with inactivated influenza vaccines do not indicate any adverse fetal and maternal outcomes attributable to the vaccine. FluQuadri should be given to a pregnant woman following an assessment of the risks and benefits. Because of the known adverse consequences of influenza infection in pregnant women, health authorities recommend vaccination of pregnant women.
Fluarix Tetra (GSK) QIIV Non-adjuncted	Use in Pregnancy: Category B1 The safety of Fluarix Tetra when administered to pregnant women has not been evaluated. A reproductive and developmental toxicity study in which female rats were administered Fluarix Tetra by IM injection (0.2 mL dose per rat, approximately 80x the human dose on the basis of bodyweight) twice prior to mating, four times during gestation, and once on lactation day 7, showed no adverse effects on female fertility, pregnancy, parturition, lactation, and embryofoetal and pre-weaning development. Vaccine antigen-specific antibodies were detected in fetuses and pups of treated rats. Fluarix Tetra should be used during pregnancy only when clearly needed, and when the possible advantages outweigh the potential risks for the mother or fetus.	Unchanged at the time of publication

Implications for other regulatory authorities

This is an example of co-ordinated public policy where government agencies and national immunization technical advisory groups (NITAGs) can work together to provide a framework and summarize the evidence to encourage pharmaceutical companies to make submissions to update product information. It also encourages pharmaceutical companies to include a consistent safety message based on the collective safety data in pregnancy. Where the evidence is supportive, vaccine product information should be accompanied by a positively worded explanation justifying the use of influenza vaccine in pregnancy, the associated positive benefit-risk profile and provide reference to national and international recommendations. This in turn is essential so that the product information documents regarding safe use in pregnancy are consistent with clinical practice recommendations, based on the best available evidence and minimize both vaccine hesitancy by the woman and the provider.

Disclosure of potential conflicts of interest

AC is co-Chair of the Australian Technical Advisory Group on Immunisation (ATAGI) and Chair of the Advisory Committee on Vaccines (ACV). MG is a member of the Australian Technical Advisory Group on Immunisation. The views expressed in this commentary are those of the authors and do not necessarily represent the views of ATAGI or ACV.

ORCID

Michelle L. Giles  <http://orcid.org/0000-0003-3007-1822>

References

1. World Health Organization. The weekly epidemiological record. Geneva: World Health Organization; 2012. p. 201–216.
2. Fell DB, Bhutta ZA, Hutcheon JA, Karron RA, Knight M, Kramer MS, Monto AS, Swamy GK, Ortiz JR, Savitz DA. Report of the WHO technical consultation on the effect of maternal influenza and influenza vaccination on the developing fetus: Montreal, Canada, September 30–October 1, 2015. *Vaccine*. 2017;25: 2279–87.
3. Shakib JH, Korgenski K, Presson AP, Sheng X, Varner MW, Pavia AT, Byington CL. Influenza in infants born to women vaccinated during pregnancy. *Pediatrics*. 2016;137(6):e20152360. doi:10.1542/peds.2015-2360.
4. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, Adrian PV, van Niekerk N, Treurnicht F, Ortiz JR, et al. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med*. 2014;371(10):918–31. doi:10.1056/NEJMoa1401480.
5. Nunes MC, Madhi SA. Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: a systematic review and meta-analysis. *Hum Vaccin Immunother*. 2018;14(3):758–66. <https://www.ncbi.nlm.nih.gov/pubmed/28708952>.
6. Burney LE. Influenza immunization: statement. *Public Health Rep*. 1960;75:944. doi:10.2307/4590965.
7. Ortiz JR, Englund JA, Neuzil KM. Influenza vaccine for pregnant women in resource constrained countries: a review of the evidence to inform policy decisions. *Vaccine*. 2011;29(27):4439–52. PMID 21550377. doi:10.1016/j.vaccine.2011.04.048.
8. Ortiz JR, Perut M, Dumolard L, Wijesinghe PR, Jorgensen P, Roper AM, Danovaro-Holliday MC, Heffelfinger JD, Tevibenissan C, Teleb NA, et al. A global review of national influenza immunization policies: analysis of the 2014 WHO/UNICEF joint reporting form on immunization. *Vaccine*. 2016 Oct 26;34(45):5400–05. doi:10.1016/j.vaccine.2016.07.045.
9. Regan AK, Mak DB, Hauck YL, Gibbs R, Tracey L, Effler PV. Trends in seasonal influenza vaccine uptake during pregnancy in

- Western Australia: implications for midwives. *Women and Birth*. 2016;29:423–29. doi:10.1016/j.wombi.2016.01.009.
10. McHugh L, Andrews RM, Lambert SB, Viney KA, Wood N, Perrett KP, Marshall HS, Richmond P, O'Grady KA, et al. Birth outcomes for Australian mother-infant pairs who received an influenza vaccine during pregnancy 2012–2014: the FluMum study. *Vaccine*. 2017;35(10):1403–9.
 11. Moberley SA, Lawrence J, Johnston V, Andrews RM, et al. Influenza vaccination coverage among pregnant Indigenous women in the Northern Territory of Australia. *Commun Dis Intell Q Rep*. 2016;40(3):E340–E346.
 12. McCarthy EA, Pollock WE, Tapper L, Sommerville M, McDonald S. Increasing uptake of influenza vaccine by pregnant women post H1N1 pandemic: a longitudinal study in Melbourne, Australia 2010–2014. *BMC Pregnancy Childbirth*. 2015;15. doi:10.1186/s12884-015-0486-3.
 13. Krishnaswamy S, Wallace EM, Buttery J, Giles ML. Strategies to implement maternal vaccination: a comparison between standing orders for midwife delivery, a hospital based maternal immunisation service and primary care. *Vaccine*. 2018 Mar 20;36(13):1796–800. Epub 2018 Feb 2. doi:10.1016/j.vaccine.2017.12.080.
 14. Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women - a systematic review. *Vaccine*. 2014 Aug 6;32(36):4602–13. doi:10.1016/j.vaccine.2014.06.067.
 15. Yudin MH, Salaripour M, Sgro MD. Pregnant women's knowledge of influenza and the use and safety of the influenza vaccine during pregnancy. *J. Obstet Gynaecol Cancer*. 2009 Feb;31(2):120–25. doi:10.1016/S1701-2163(16)34095-6.
 16. Top KA, Arkell C, Scott H, Mannerfeldt J, Ortiz JR, Lambach P, MacDonald N. Effect of package insert language on health-care providers' perceptions of influenza vaccination safety during pregnancy. *Lancet*. 2016 Oct;4(10):e690.
 17. Proveaux T, Lambach P, Ortiz JR, Hombach J, Halsey NA. Review of prescribing information for influenza vaccines for pregnant and lactating women. *Vaccine*. 2016;34:5406–09. doi:10.1016/j.vaccine.2016.08.042.
 18. https://www.who.int/biologicals/areas/vaccines/Executive_summary_FINAL_labeling_Sept_mtg_16_Dec_2015.pdf?ua=1.
 19. European Medicines Agency. Evaluation of Medicines for Human Use. Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling. London, UK. 2008 July 24.
 20. Food and Drug Administration, HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. *Fed Regist*. 2014 Dec 4;79(233):72063–103.
 21. Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. *Hum Vaccin Immunother*. 2019;15(3):687–99. Epub 2018 Nov 15. doi: 10.1080/21645515.2018.1540807.
 22. <https://www.fda.gov/media/119856/downloadFluzoneQuadrivalentProductInsertUnitedStates>.
 23. <https://medicines.org.au/files/swpfluqu.pdfFluQuadriProductInsertAustralia>.
 24. <https://www.medicines.org.uk/emc/product/666/smpc#PREGNANCYFluQuadriProductInsertEurope>.