Executive Summary

WHO working group meeting on labelling information of influenza vaccines intended to be used in pregnant women

24-25 September 2015 Geneva, Switzerland

Summary
Activities that support evidence based use of vaccines during pregnancy are important elements of the WHO initiative to improve maternal and child health. Existing inactivated influenza vaccines (IIV) have been shown to be safe and effective in healthy adults and children. Maternal influenza immunization has been also shown to protect pregnant women and their infants in the first few months of life. Nevertheless, there is reluctance on the part of many vaccine program administrators and expectant mothers to use these vaccines.

This is, at least in part, due to the fact that the approved labelling information and package insert (PI) do not include an indication for use during pregnancy. There is no international standard for layout and content of the PI. Where the PI addresses the use of IIVs in pregnant women, it is in a section on special populations and the wording usually recommends caution.

This meeting was called to review the wording in several PIs and to explore the possibility of providing a guidance document to help the interpretation of the information in Pregnancy subsection of IIV PIs.

The background morbidity and mortality caused by influenza disease during pregnancy and the available reports from studies of the safety on IIVs was presented together with survey results indicating that the misinterpretation of the wording in the PI could limit the use of the vaccines in this target population.

Regulatory policy and practices with regard to the permitted text in the PI sections on pregnancy & lactation (P&L) were described from the EU, USA and Canada, followed by similar presentations from Brazil, Indonesia, India, Thailand and Ghana. The results were presented from a 2014 survey of the WHO Developing Countries Vaccine Regulators’ Network on the regulatory policies and perceptions of the wording of the PI related to influenza vaccine use during pregnancy. These presentations showed the diversity of approach and understanding in different countries and regions.

Issues raised in discussions included:

- National expert advisory groups and the WHO Global Advisory Committee on Vaccine Safety have reviewed the available evidence and concluded that the benefits of using current IIVs during pregnancy far outweigh any known, reported or potential risks. Systematic reviews of influenza vaccine safety in pregnancy support this conclusion.

- The WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommends influenza vaccine prioritization for pregnant women for countries with an influenza vaccine program or intending to maximize the impact of influenza vaccination. There is no preference for trimester for vaccine receipt.
• There is no evidence or consideration that use of IIV in pregnant or lactating women is a risk to the infant.

• The implementation of the EU required-text for IIV PI that classifies all EU licensed IIV as similar with regard to safety in pregnant women and encourages use at any stage of pregnancy was considered.

• In the majority of countries, the format and content of the PI is defined in law, and the information in the PI is approved by the national regulatory authority (NRA), supported by data from clinical trials or post-marketing experience, and is product-specific, so that without this evidence there can be no PI indication for use. However, even when this evidence is lacking for a specific product, the IIVs are recommended for use in pregnant women by the national public health authorities, and this is not considered off-label use.

• The recent revision of the US FDA labelling requirement and regulations to address pregnancy and lactation – the pregnancy and lactation labelling rule (PLLR) implemented June 30, 2015, was described. The most significant change to be implemented by this Rule is the removal of the letter risk categories A, B, C, D and X from all labelling, replacing them with a narrative summary of the risks of using a drug or biological product during pregnancy. These summaries will be based on available human and/or animal data and will be accompanied by a discussion of the data.

• In countries that import IIVs, the format, data and language included in the PI usually reflects the text approved by the NRA in the respective manufacturing country following its national regulation. NRAs in some countries have required the addition of language that makes the cautionary language for use even stronger. In addition the P&L section may be included in the warnings and precautions section of the PI, e.g. in Brazil and Indonesia. National vaccine program administrators, health care providers, and patients may be misinterpreting the information as a contraindication for use.

• Live influenza vaccines are not contraindicated for use in pregnant women in India.

• The apparent reluctance of manufacturers to encourage use of IIV in pregnant women is an important constraint, as it is usual for the manufacturer to initiate any revision of the PI text, and provide evidence in support any extension of use. This may be due to uncertainties regarding strength of reporting systems to capture and to determine causality assessment of adverse events following immunization, lack of knowledge of the legal environment and systems in countries that do not routinely use influenza vaccines.

• The seasonality of IIV supply and the fact that immunization of pregnant women may be required outside of usual periods of vaccine availability before the influenza season. Seasonal vaccines only become available following the processes of annual strain selection and the approval of the IIV for the future influenza season.
• The unsuitability of a new WHO prequalification (PQ) Model PI to encourage manufacturers to include suitable text for IIV use during P&L.

• NRAs considered that product specific evidence is required to support the statements in the PI. Regulators were concerned that wider adoption of the EU class-approach for IIVs in non-EU countries would be unsuitable, as the EU had not evaluated vaccines from other (& emergent) manufacturers not represented in EU, nor the differing environmental conditions that may influence the safety or reactogenicity of vaccines in other regions.

• Although a few countries have a specific contraindication for use of IIVs in pregnant women, the wording of the PI P&L sections in most of the different countries does not constitute a contraindication for use and the national vaccine program administrators, health care providers, and patients may be misinterpreting the information.

Conclusions:
- It was considered that guidance from WHO could help clarify the benefits of vaccination during pregnancy as set out in the PI.

- The working group did not recommend (EU-like) class recommendations, as the EU had not evaluated vaccines from other (& emergent) manufacturers not represented in EU, nor considered differing environmental conditions that may influence the safety or reactogenicity of vaccines in other regions. Participants agreed that product specific recommendations were appropriate.

- WHO PQ group confirmed that the Model package insert example for IIVs is not a useful tool for encouraging IIV use in pregnant women.

- This guidance could be in the form of an addendum to the existing WHO Technical Report Series (TRS) 927 on Inactivated Influenza Vaccines, outlining the important information to be included in the PI and the extent of evidence that would be required by regulatory authorities to include recommendations for use of the IIV vaccines in pregnant women.

- The purpose of the document is to clarify and interpret the information of the Pregnancy subsection of IIV PIs. More defined WHO recommendations or guidelines could conflict with national legal requirements for the format of a PI.

- Drafting group members were agreed and sections assigned for drafting: Dr E Griffiths, Dr M Gruber, Dr H-N Kang, Prof P Neels, Dr M Pfleiderer, and Dr J Southern.
Agreed outline and content of Addendum to TRS 927:

- Introductions (to be drafted by Dr E Griffiths)
  - MI in Public Health
  - Importance of IIV MI in Global Immunization
  - WHO Sage advice
  - Example of Tetanus and aP.

- Background (to be drafted by Dr E Griffiths)
  - Current IIV P&L labelling regulatory-permitted,
  - Compliance with law – PI format – P&L text
  - NITAG Advice (ACIP, NACI), explain differences between NRA and NITAG
  - WHO PQ approach to label – reliant on NRA approval
  - Survey results of PI, including misinterpretation of P&L advice
  - Repeat SAGE recommendations, statement of problem

- Scope (to be drafted by Dr E Griffiths)
  - SIV, but some explanation about live, adjuvanted one; expand to other vaccines, e.g. Td
  - Objective: To explain, clarify, and raise awareness
  - Target Audience: Manufacturers, NRA, end-user Program managers & NITAG

- Glossary (to be drafted by Dr H-N Kang)

- Subsection (to be drafted by Dr M Gruber)
  - PI – explain purpose of PI
  - Describe purpose of the following section and how they differ
    - Indications
    - Contraindications
    - Warnings & Special precautions
    - Special population
      - Pregnancy and Lactation section
        - Data supporting an indication statement vs data to be included in the pregnancy subsection of the PI
        - Explain how recommendations made by public health advisory bodies differ from what can be included in an NRA approved PI.
        - Example of current language used in pregnancy subsection (Dr J Southern)

- Conclusion (to be drafted by Prof P Neels)
  - Interpretation: detail explain what the information means.
Agreed timeline:

- Present the outline of doc at the ECBS, 12 Oct 2015
- A drafting group to prepare each section, by end October 2015
- Discussion about assembled text at DCVRN, 12-16 Nov 2015
- Drafting group to complete the 1st draft, by end Nov 2015
- 1st round of public consultation, Dec 2015- Jan 2016
- Informal consultation, 4-5 April 2016
- Drafting group to prepare the 2nd draft, by end June 2016
- Submit to the ECBS 2016, by mid July 2016
- 2nd and final round of public consultation, July – Sept 2016
- Discussion at the ECBS 2016, Oct 2016.

Working Group
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10. Knowledge and attitudes of pregnant women and their providers towards recommendations for immunization during pregnancy, Vaccine Volume 33, Issue 41, Pages 5333-5488, 5 October 2015. 

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