Executive Summary

WHO consultation on influenza vaccines for pregnant and lactating women: Clinical data requirements for product labelling
15 – 16 July 2014 Geneva, Switzerland

Introduction
Immunization is an increasingly important strategy to protect pregnant and lactating women and their infants against influenza and other vaccine preventable diseases. However, the introduction of influenza vaccination into antenatal vaccination programs has been slow, and influenza virus continues to cause disease and death in this population. The cautious wording regarding vaccine safety in pregnancy on the product label may contribute to reluctance by countries to implement maternal influenza immunization programs.

The Consultation held at WHO Headquarters on 15-16 July 2014 was organized by the Technology, Norms and Standards team and Initiative for Vaccine Research team to review current approaches for labelling of inactivated influenza virus (IIV) vaccines intended for use in pregnant and lactating women. The current style of the wording for labelling, package insert and prescribing information of pregnancy and lactation (PI P&L) was discussed in the context of regulatory and manufacturing practices. The similarity of the IIV product quality, immunogenicity and reactogenicity was explored to identify possible classes of IIV vaccines that could share similar PI P&L advice. The meeting reviewed current approaches for clinical data submission for labelling, and it explored the possibility of using data from prelicensure clinical trials and from other sources such as postmarketing surveillance, pregnancy registries and observational studies – even with other makes of IIV. In addition relevant WHO guidance documents were reviewed to identify gaps in the guidance for product labelling regarding the use of vaccines in pregnant and lactating women. Although the discussion was focused on the situation with the IIV vaccines, it was recognized that other vaccines such as acellular pertussis also need to be addressed by WHO in future.

Maternal immunization: Public health perspective
The WHO Strategic Advisory Group of Experts (SAGE) has recommended vaccination of pregnant women with IIV vaccines as an effective and safe intervention to decrease influenza-related morbidity and mortality during pregnancy, a benefit also extended to the newborn [Vaccines against influenza. WHO position paper – November 2012. WER 2012;87(47):461-476], and it has urged that efforts be made to improve coverage with seasonal influenza vaccines. Possible measures to improve the implementation of this recommendation have been the subject of several reports, collated by the Global Advisory Committee of Vaccine Safety and presented to SAGE in 2013.

Recent clinical data revealed that immunization of pregnant women can confer protection against influenza disease to newborns during the first six months of life. Despite WHO recommendations, maternal influenza immunization has not been incorporated into routine immunization programs in many low-income countries. Therefore, WHO has been tasked to examine this problem; including the examination of the role of the wording of the prescribing information, permitted by regulatory authorities, that may discourage decision makers from including these vaccines in antenatal health programmes [Meeting SAGE, November 2013 – conclusions and recommendations. WER 2014;89(1):1-20].
WHO was requested to engage in “a dialogue with regulators and manufacturers to review current regulatory practices against the evidence on risks and benefits and biological plausibility on product safety”. This meeting is part of these activities.

**Immunization during pregnancy: Examples of influenza vaccines**

Implementation of influenza immunization remains suboptimal as national immunization program decision makers often lack information on the relative impact of strategies for vaccine implementation;

For example:

- Lack of information on the national burden of influenza mortality and morbidity in pregnant women and infants
- Other obstacles to immunization that can include the perceived risks of influenza vaccines in this group
  - This is, in part, related to the precautionary language of PI that sets out the available evidence and may imply a greater vaccine risk than is known.

Some regulatory authorities require that the indications for influenza vaccines do not include pregnant and lactating women, since there is no substantial evidence of efficacy and safety derived from controlled clinical trials in such populations, and this evidence is currently not available as, traditionally, pregnant women have been excluded from the clinical trials.

WHO Pre-qualified (PQ) IIV vaccines include PI P&L information that reflects the regulations of the national regulatory authorities in the country of manufacture. The PI advice is based on product specific clinical trial evidence and is generally precautionary, e.g. *should be used only following the advice of a healthcare professional, based on consideration of the benefits and risks to the mother and the foetus*. One PQ IIV vaccine includes positive advice based on general clinical experience with IIV vaccines, but still cautions “*If pregnant, please inform your doctor or pharmacist*”.

National immunization programme managers may interpret these statements as cautions against the vaccine use in pregnant women; this represents a significant challenge to implementing immunization of pregnant women against influenza. This is evident even in countries where the National Immunization Advisory Groups have strongly advised in favour of IIV vaccination of pregnant women.

**Influenza vaccine labelling: key issues from regulatory and manufacturers’ perspectives**

The labelling requirements for influenza vaccines in the EU, USA and Canada were described, particularly the wording and language permitted in the label PI sections on vaccine use during P&L. There was a variability between countries.

Following evaluation of all the available evidence, relating to the quality, safety and efficacy of IIV vaccines, especially data collected during postmarketing surveillance in the EU [ECDC scientific advice on seasonal influenza vaccination of children and pregnant women 2012], the EMA has advised that licence holders of all egg-derived IIV vaccines should amend the PI P&L section to include the following statement.

_Inactivated influenza vaccines can be used in all stages of pregnancy. Larger datasets on safety are available for the second and third trimester, compared with the first trimester; however, data from worldwide use of inactivated influenza vaccines do not indicate any adverse foetal and maternal outcomes attributable to the vaccine_
This is a positive recommendation for all the egg-based IIV “class” of vaccines. Such a class recommendation is unprecedented for use with vaccines. The EMA regulatory approach to seasonal IIV vaccines is under review; a guideline is due to be published that will include enhanced safety surveillance for all influenza vaccines and product-specific effectiveness studies. These studies will include vaccinated pregnant women, and standard defined end-points will be used.

In contrast the US FDA has required prescribed text based on the available evidence for each individual IIV vaccine product. Current FDA regulations require that each drug or vaccine is classified under one of five pregnancy categories (A, B, C, D or X), based on the extent of nonclinical and clinical supporting evidence of risk of reproductive and developmental adverse effects, or risk weighed against potential benefit for certain categories. The specific PI P&L text for each category is prescribed by regulation. This text includes a summary of the supporting evidence and cautionary statements recommending benefit-risk assessments, e.g. “Use only when clearly needed”. The text does not contraindicate use of the IIV vaccines for pregnant women, and the prescribed text is intended to ensure that vaccine users are fully informed of the available information for each individual product and that vaccinators consider the risks and benefits of IIV vaccination.

When these vaccines are imported into other countries it is common to include similar wording, sometimes adapted to local conditions.

The FDA is in the process of revising its current rules and regulations to remove the letter categories, which would be replaced by a summary of the risks of using a drug during pregnancy based on available human and animal data and a description of these data. In addition, the rule would require that the prescribing information include relevant clinical information to help health care providers make prescribing decisions and counsel women about the use of drugs/vaccines during pregnancy.

The situation with regard to label policies in other countries was considered and although many regulatory authorities will permit inclusion of text from National Immunization Advisory Groups that encourages IIV immunization of pregnant women, cautionary statements remain common.

In developing countries, it was reported that although the IIV vaccines were not included in routine public health immunization programmes, they were licensed for use; generally with the same prescribing information that had been required by the national regulatory authority in the country of manufacture, so that vaccines that had been licensed in the USA would carry the same cautionary statements.

The representatives of the manufacturers were concerned that including text that was not supported by evidence could result in liability claims in the event of adverse outcomes if used during pregnancy, even in regions where the national regulatory authority has required text supporting use of the vaccine. Developing Country Vaccine Manufacturers Network representative highlighted that as IIV vaccines are not included in the public health immunization program, there is a reluctance to include pregnant women in clinical trials and there are no national or international guidelines for influenza vaccine use in pregnancy, manufacturers see this as relatively low priority at this stage. Leadership from WHO would promote these activities.
Although each individual make of influenza vaccine uses different manufacturing technologies, there are significant overlaps in product quality that could be considered as supportive of class-recommendations regarding the safety of the vaccine in pregnant women.

The value of using the WHO PQ process to encourage appropriate PI and label changes was discussed. This would be of particular value in the developing country setting when IIV vaccines are introduced. It is possible to develop a Model Package Insert for IIV vaccines (similar to that already used for other vaccines) that could include suitable wording to encourage use of the vaccines during pregnancies and that would explain the basis for such statements. It was suggested that Programmatic Suitability Criteria for acceptability of new IIV vaccines could be amended to include “evidence of safety for use in pregnant women”. The difficulties with this approach regarding requirements for vaccines that are already pre-qualified are recognized.

The position regarding the labelling of other vaccines that are commonly used during pregnancy was briefly considered. The position for tetanus vaccines is a general acceptance that all these vaccines will be safe and effective and confer a definite benefit in developing countries. The position with other types of vaccine varies, but the information approved in the PI P&L is generally product specific and cautious.

**Conclusions and way forward**

The meeting recognized that, based on the information from SAGE and other expert bodies, there is no evidence to suggest a different safety or immunogenicity profile of any currently available IIV vaccine in pregnant women, relative to the standard adult population in which licensure studies had been conducted. However, there has been a tendency, based on the vulnerability of pregnant women and the lack of specific data, for regulatory authorities to require cautionary statements in the PI and label that may limit the use of these vaccines.

A substantial number of postmarketing studies and surveillance data support the safety and effectiveness of IIV (and pandemic) vaccines in pregnant women and show benefits for the foetus and new-born infants. Further prospective randomized controlled clinical trials in this population are ongoing in a number of countries for one widely-used IIV vaccine and these results will be published soon. These results may provide further support for the positions below.

The current wording permitted in the IIV vaccine Prescribing Information for special populations – Pregnancy & Lactation in the European regulatory region has been recently revised to be overtly supportive of use during pregnancy, even without product-specific information. This approach is based on the consideration that the IIV vaccines (licensed for use in EU) have a record of safety of use in pregnant women and may be considered a “class” for regulatory purposes. However, future revisions of the guideline may change this policy.

The US FDA prescribing information with regard to the pregnancy subsection is currently cautionary but does not contraindicate use of IIV vaccines in pregnancy. The proposed revisions of the FDA regulations regarding the pregnancy subsection of the labelling, when finalized, will require a summary of human data concerning the vaccine’s effect on pregnant women and their offspring to be included in the labelling. Sources of human data may come from clinical trials, pregnancy exposure registries,
epidemiologic studies, or case series. While this information will most likely remain product specific it will include information on the benefits of IIV vaccine use in pregnant women.

Other national regulatory authorities follow one or the other of the above policies – or accept the wording of the imported IIV vaccine, as required in the country of origin. This is particularly the case in developing countries, and the adoption of labelling policies similar to the EU by the WHO PQ process may promote the acceptance of IIV vaccines in countries where vaccines are supplied by UN agencies.

It was suggested that the WHO PQ process for vaccines could be explored as a starting point for improving the acceptability of vaccines for immunization of pregnant women by including a requirement for suitable evidence in the Programmatic Suitability Criteria and developing a Model Package Insert for new applications for IIV vaccines that includes text supporting the use of suitable vaccines in pregnant women. For existing PQ IIV vaccines, a process would need to be developed to include changes in the PI that would help promote the acceptance of IIV vaccines in developing countries.

- Text recommending a class approach to use of IIV vaccines in pregnant women, similar to that permitted by the EMA, could be included in a Model Package Insert for IIV vaccines – as used for other PQ vaccines.
- Discussion is needed on how this could be implemented for vaccines that are already prequalified.
- Where PQ vaccines are supplied by UN Agencies, each recipient country will apply a suitable evaluation and license procedure for the supplied vaccine – this will need to include the acceptability of the WHO PQ Model Package Insert.

The current WHO revision of “Guidelines on Clinical Evaluation of Vaccines: Regulatory expectation (WHO TRS 924)” should include an updated section explaining the rationale for clinical studies in pregnant women where there is evidence of safety in the general population and where the vaccine may be of benefit to pregnant women and their infants.

All WHO supported meetings and consultations with regulatory authorities should address the use of IIV vaccines in pregnancy and related PI information.

There is a need for added country-specific data on the burden of influenza disease particularly in pregnancy and new-born infants, and in developing countries. This point should be raised in relevant meetings, e.g. Developing Country Vaccine Regulators’ Network or African Vaccine Regulatory Forum.

The possible relationship between IIV vaccine reactogenicity in infants (Australian experience) and safety in pregnant women should be explored. This is considered to be not linked by some experts, but the evidence for this is unclear.

There is an issue of the consistent availability of IIV vaccines for maternal immunization in equatorial developing countries due to the seasonal changes in the virus strains by manufacturers and possible discordance of in-country influenza incidence with availability of Northern or Southern hemisphere vaccines. This is linked to the need for extended stability data supporting a longer shelf-life. The relevant countries should be supported in efforts to gather this data.
The link between antibody levels following IIV vaccination and vaccine efficacy needs further investigation.
The continued suitability of haemagglutinin antibodies, (1:40 titre) as a measure of immune response and correlate of protection, needs to be confirmed, particularly in pregnancy.

The types of non-clinical and clinical studies on individual IIV vaccine products that support the class approach to vaccine labelling that is currently accepted in the EU should be considered for existing IIV vaccines, and for new IIV vaccines.

Key findings relating to the use of vaccines in pregnant women:
- Regulators approve or permit the wording in package inserts or label. This wording is submitted by manufacturers based on the evidence provided to support the license application.
- In the PI subsection for use in pregnant and lactating women, precautionary statements may be required by regulators to reflect the available evidence of safety, but they are not intended as barriers for use.

Key findings relating to IIV vaccines used in pregnant women.
- Wording in the PIs of EU and USA already allows the use of IIV vaccines in pregnant women – but this is not always clearly stated.
- The PI subsection cautionary statements can be misinterpreted by vaccine users and immunization program managers as a warning against use of IIV vaccines in pregnant women.
- Communication on the meaning of these statements needs to be improved for the benefit of policy makers and other relevant parties.
- Some regulators, e.g. in USA and EU are taking steps to improve how the information is presented in subsections for use of IIV vaccines in pregnancy.
- Class labeling approach based on the history of safe IIV vaccine use during pregnancy has been accepted in the EU.

Abbreviations and Acronyms
DCVMN  Developing Country Vaccine Manufacturers Network
EMA  European Medicines Agency
EU  European Union
FDA  Food and Drug Administration
IIV  Inactivated Influenza virus
PI  Package Insert/Prescribing information
PQ  Prequalification for supply to UN Agencies
P&L  Pregnancy and Lactation
SAGE  Strategic Advisory Group of Experts (WHO)
TRS  Technical Report Series (WHO)
UN  United Nations
USA  United States of America
WER  Weekly Epidemiological Record
WHO  World Health Organization