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PROPOSED ADDENDUM TO: Annex 3 of WHO Technical Report Series, No. 927

Recommendations for the production and control of influenza vaccine (inactivated)

APPENDIX 4. LABELLING INFORMATIONOF INACTIVATED INFLUENZAVACCINESFOR USE IN PREGNANT WOMEN

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this draft is to provide information about the proposed WHO document on *Labelling Information of Inactivated Influenza Vaccines for Use in Pregnant Women* to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text MUST be received by 23 September 2016 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Hye-Na Kang at email: kangh@who.int.
The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (KMS/WHP/13.1).

This guidance document published by WHO is intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, this document may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to this document be made only on condition that the modifications ensure that the product is at least as safe and efficacious as that prepared in accordance with the principles set out below.

Contents

1. Introduction

Morbidity and mortality due to seasonal influenza virus infection are considered substantial worldwide *(1, 2)*. Pregnant women are especially vulnerable. They have an increased risk of severe disease and death from influenza, and the infection may also lead to fetal complications such as stillbirth, neonatal death, preterm delivery and decreased birth weight *(3, 4)*. For these reasons, in 2012 the WHO position paper on vaccines against influenza *(3)*, endorsed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE), recommended the immunization of pregnant women with trivalent inactivated influenza vaccine (IIV) at any stage of pregnancy *(3)*. SAGE also recommended that pregnant women should have the highest priority for countries considering the initiation or expansion of immunization programmes for seasonal influenza vaccination *(3, 5, 6)*. The recommendation is based on evidence of a substantial risk of severe disease in this population group and evidence that the use of seasonal influenza vaccine is both safe throughout pregnancy and effective in preventing influenza in women as well as in their young infants in whom the disease burden is also high *(3, 5)*. After careful analysis of data worldwide, the WHO Global Advisory Committee on Vaccine Safety (GACVS) concluded that there was no evidence of adverse pregnancy outcomes associated with the vaccination of pregnant women with several inactivated viral or bacterial vaccines, including IIVs *(5, 6)*. However, for various reasons, the implementation of influenza immunization during pregnancy remains suboptimal *(4)*. One reason is the perceived risk of administering influenza vaccine, or indeed any vaccine, to this population group particularly because of the precautionary language used in some product labels and the likelihood of misinterpretation.

The development of this explanatory addendum arises from the recommendations of SAGE regarding the advice to immunize pregnant women with IIV and the resulting discussions of several WHO consultations *(3,6–8)*, as well as discussions at the Sixty-sixth meeting of the WHO Expert Committee on Biological Standardization in 2015 (*9*).

2. Background

Activities to enhance the uptake of vaccines during pregnancy are important elements of WHO's ongoing initiative to improve maternal and child health. As part of this work, WHO held a consultation in July 2014 on influenza vaccines for pregnant and lactating women which focused on the clinical data requirements for product labelling information *(8)*. The consultation was

organized by the WHO team for Technologies, Standards and Norms and the WHO Initiative for Vaccine Research and brought together regulators, manufacturers and researchers with experience in vaccines. A further consultation was organized by the WHO Technologies, Standards, and Norms team in 2015 to review existing guiding principles and regulations relating to product package information for IIVs and to explore the possibility of developing an addendum to the existing *Recommendations for the production and control of influenza vaccine (inactivated) (10)* with the aim of clarifying and interpreting the subsections of labelling information so as to facilitate uptake of IIVs in pregnancy *(7)*. Regulatory policy and requirements regarding permitted text in product insert sections on pregnancy and lactation were reviewed from selected developed and developing countries (Brazil, Canada, European Union (EU), Ghana, India, Indonesia, Thailand and the United States of America). Also presented were the results of a 2014 survey of the WHO Developing Country Vaccine Regulators' Network regarding regulatory policies and the interpretation of the wording in the pregnancy and other subsections of IIV labelling. The diversity of approach and understanding in different countries and regions was evident. It also became clear that, in countries which import IIVs, the format, data and language included in the product insert usually reflected the text approved by the national regulatory authority (NRA) in the respective country of licensing. Some developing countries require additional language that makes the perceived cautionary message for use even stronger. The regulatory position is based on the fact that licensing is product-specific and is reliant on data generated during the clinical evaluation of the vaccine and submitted by the manufacturer. The European Medicines Agency (EMA) implemented a policy based on an evaluation of all available evidence on the safety and effectiveness of IIVs and expected all IIV licence holders in the EU to amend the pregnancy subsection of the labelling to include advice that IIVs can be used during all stages of pregnancy (*8*). However, with the guideline on influenza vaccines entering into force, the EMA now requires that product-specific data be generated in appropriately designed studies with each IIV (*11, 12*).

Some NRAs include recommendations made by national public health advisory bodies on the use of IIVs in pregnancy to protect mother and infant against influenza *(13–15)*, thus adding to the confusion regarding what the information in the label means. Even though the wording in the package insert for IIVs does not represent a contraindication to the use of the vaccines in

pregnancy, the particular wording employed is often misinterpreted to imply a contraindication. Consequently it is interpreted as differing from statements made by advisory bodies such as national immunization technical advisory groups (NITAGs) and SAGE recommending use of IIVs in pregnancy to protect mother and infant from the disease. Thus there is a perceived contradiction between the statements of advisory bodies and the position of the NRA.

NITAGs' recommendations on use of the vaccine in pregnancy are made on the basis that the benefit of vaccination in pregnant women usually outweighs the risk of potential adverse effects in the mother or developing offspring when the risk of disease exposure is high, when the infection poses a special risk to mother and fetus and when the vaccine is unlikely to cause harm. In contrast, a statement in the "Indications and Usage" section of the labelling that specifically addresses use of the product in pregnancy can be approved by an NRA only when data from adequate and well-controlled studies in pregnant women are available to support the statement. Pregnant women are usually excluded from clinical studies during vaccine development, so licensure dossiers generally do not include information on safety and efficacy of the particular vaccine in pregnant women. In the absence of such data, therefore, the "Indications and Usage" section of the label will lack a statement that specifically describes use of the product in pregnancy.

3. Purpose

The aim of this addendum is to provide clarification and interpretation of the labelling information provided in the product insert of IIVs in order to facilitate maternal immunization programmes. It is also intended to raise awareness of the convergence of regulatory positions in spite of differing approaches to labelling and regulatory language regarding the use of these vaccines in pregnant women. On the basis of current evidence, the use of IIV in pregnant women is not contraindicated.

4. Scope

This document applies to inactivated trivalent and quadrivalent (tetravalent) influenza vaccine for which sufficient safety data are available. It is intended for NRAs, manufacturers, end-user programme managers and NITAGs.

Liability issues are beyond the scope of this document.

5. Terminology

The definitions given below apply to the terms as used in this document. They may have different meanings in other contexts.

Summary of product characteristics (SmPC): The SmPC is the basis of information for health-care professionals on how to use the medicinal product safely and effectively. The labelling should be drawn up in accordance with the SmPC.

Label(ling): All forms of product information – i.e. container label, product/package insert, package leaflet and prescribing information.

Maternal immunization: Frequently used to refer to vaccination prior to, during, or after pregnancy. For the purposes of this document, "maternal immunization" refers to vaccination during pregnancy.

National Immunization Technical Advisory Group: A national expert advisory group that evaluates the available evidence of national disease incidence, and available vaccines, to provide advice to the health ministry on the national immunization programme's policies and on priority vaccines and target populations.

6. Labelling information

Like all prescription drugs and biological products, IIVs must be accompanied by labelling that summarizes scientific information concerning the safe and effective use of the product.

Labelling includes the package insert, which is also referred to as prescribing information or the summary of product characteristics (SmPC) *(16)*. This component of labelling is the primary mechanism through which regulatory agencies and vaccine manufacturers communicate essential, science-based information that is used by health-care professionals in making prescribing decisions and in counselling patients about the risks and benefits of a product. The content and

format requirements for labelling are prescribed by regulations specific to the country where the vaccine is licensed and may differ between countries *(16, 17)*. Nevertheless, common principles include that prescribing information should be based on available data, that it must not be misleading, and that it must not contain implied claims or uses for which there is inadequate evidence of safety or effectiveness *(18)*.

The sections of labelling that are relevant to the use of vaccines in pregnancy – namely, "Indications and Usage", "Warnings and Precautions", "Contraindications", and "Use in Specific Populations" – are described below. Countries have information on vaccination in pregnancy under various sections. Information regarding the use of an IIV in pregnancy is typically found under the "Use in Specific Populations" section. However, in some countries the NRA has required that precautionary statements about the use of an IIV in pregnancy should be included under the "Warnings and Precautions" and "Contraindications" sections because safety data on use of the vaccine in pregnancy may be unavailable or insufficient.

6.1 Indications and Usage

The "Indications and Usage" section of labelling communicates a product's approved indication(s) and should clearly convey the use(s) for which the product has been shown to be safe and effective. Although pre-licensure clinical trials are generally conducted in carefully selected populations, the "Indications and Usage" statement(s) often reflect a broader population and take into consideration the generalizability of the evidence. Typically, for preventive vaccines, the "Indications and Usage" statement(s) state the disease being prevented and the age range for which use is approved.

Specific regulatory requirements and standards for demonstrating that a vaccine is safe and effective may vary between NRAs. However, in general, the standards for demonstrating the safety of a vaccine for its intended indication take into consideration the condition of the recipients and the characteristics of the product. It is expected that pre-licensure data demonstrating that a vaccine is effective for the intended indication and use are derived from adequate and well-controlled clinical studies. Data from pregnancy exposure registries, epidemiological studies and case series are typically collected in the post-marketing period and are used to inform the "Use in Specific Populations" section of the labelling (see Section 6.4).

While data from related, similar vaccines may be supportive of an indication for use, it is typically expected that the specific vaccine is evaluated for safe and effective use in the intended population. For most IIVs that are currently licensed, data from adequate and well-controlled studies demonstrating that vaccination during pregnancy is safe and effective for the pregnant woman or newborn infant may not be available to support an indication in the labelling. Data from studies published in the literature about use of IIV in pregnancy may not have been submitted to NRAs or may not meet regulatory requirements. In such cases, product(brand)-specific data demonstrating that the vaccine is safe and effective may not be available. Consequently, the prescribing information for IIVs does not include an "Indications and Usage" statement that specifically addresses use in pregnancy. This does not mean, however, that IIVs are contraindicated for use in pregnancy. IIVs are licensed for use in an age range that includes women of childbearing age. In the absence of evidence that the risk of use in pregnancy clearly outweighs any possible benefit, there is no specific contraindication for use in pregnancy and, consequently, IIVs may be administered to pregnant women. Available data specific to the use of IIVs in pregnancy will be included in the "Use in Specific Populations" section of labelling (see Section 6.4).

6.2 Warnings and Precautions

The "Warnings and Precautions" section of the product labelling is intended to include, but is not limited to, a description of adverse events that are serious or otherwise clinically significant because they have implications for decisions on prescribing or for the management of patients. For an adverse event to be included in this section, there should be reasonable evidence of a causal association between the adverse event and the drug or biological product.

Clinically significant adverse reactions that have not been observed following use of the specific drug or biological product, but are anticipated on the basis of data on another drug in the same class, or animal data, should be included under "Warnings and Precautions". Clinically significant interference with laboratory tests, clinically significant drug interactions, and any special care or monitoring required to ensure safe use also should be included under "Warnings and Precautions". The description of each adverse reaction or topic included under "Warnings and Precautions" is cross-referenced to a more detailed discussion of the risk elsewhere in the

labelling (e.g. in "Adverse Reactions" and "Use in Specific Populations"). Some NRAs require the inclusion of information about use of IIVs during pregnancy in the "Warning and Precautions" section of labelling.

6.3 Contraindications

Although the specific wording used in the "Contraindications" section of the product label may depend on the requirements of the NRA where the vaccine has been licensed, there is a common requirement that drugs or biological products, including vaccines, should be contraindicated only in those situations where the known risk from use clearly outweighs any possible benefit. Only known hazards, not theoretical possibilities, should be the basis for contraindication. As an example relating to use in pregnant women, evidence in humans or animals that the vaccine poses a serious risk of developmental toxicity during pregnancy would usually warrant a contraindication for use during pregnancy. However, for IIVs as well as other vaccines, if available animal or human data do not indicate a risk in pregnancy that clearly outweighs benefit or if data are unavailable to inform risk in pregnancy, there should not be a contraindication for use during pregnancy.

6.4 Use in Specific Populations

The "Use in Specific Populations" section of labelling summarizes important differences in the response of the product, or in recommendations for use, in specific populations. Information relevant to the use of a product during pregnancy is generally found under this section and is sometimes referred to as the "Pregnancy subsection" of product labelling. However, depending on the labelling requirements of the NRA where the vaccine was licensed, information regarding the use of IIV in pregnancy may also be found in other sections of product labelling, such as the "Warnings and Precautions" section *(7)*.

The pregnancy subsection of the product labelling includes data, when available, from reproductive toxicity studies conducted in animal models to assess the potential developmental and reproductive risks of the product. Data that may be available concerning the safety of the product in pregnant women are also described in this section. Sources of human data may include pregnancy registries, pre-licensure clinical trials in which pregnant women were inadvertently exposed to the product, large-scale epidemiological studies, and case-series

reporting of rare adverse events. In general, information regarding use of IIVs during pregnancy is derived from post-marketing studies (e.g. via registries and/or from maternal immunization studies published in the literature). The quality and quantity of data from specific sources will be evaluated by the NRA to determine whether the data are scientifically acceptable for inclusion in the pregnancy subsection of the labelling. In some countries, the NITAGs' recommendations are included in this section.

As with other sections of the product labelling, country-specific requirements prescribe the information, and frequently the specific wording, to be included in the pregnancy subsection on what is known about the risks of using the product in pregnancy.

WHO's prequalification evaluation of the prescribing information is evidence-based and takes into consideration the prescribing information approved by the NRA of record for prequalification (generally the NRA in the country of manufacture).

Required statements included in the pregnancy subsection of the labelling have often been precautionary (e.g. "*should be used only following advice of a health care professional"*, *"if pregnant, please inform your doctor or pharmacist"*, *"use only if clearly needed"*. The rationale for requiring such language has largely stemmed from a lack of data from well-controlled clinical trials and not evidence suggesting specific risks of vaccination during pregnancy. Such precautionary language has sometimes been misinterpreted to mean that pregnancy is a contraindication for use.

While many NRAs require that labelling includes such precautionary language regarding use in pregnancy, some countries are considering ways to improve the clarity of the information included in the pregnancy subsection of the labelling. For instance, the United States Food and Drug Administration has recently revised its labelling regulations so that they no longer require such precautionary language *(17, 19).* With implementation of the Pregnancy and Lactation Labeling Rule in the USA in June 2015 *(17),* the revised regulations now require that the pregnancy subsection of labelling includes narrative summaries of the risks of a product during pregnancy and discussions of the data supporting those summaries. Under the revised regulations, labelling will include relevant available clinical information from use of the product in pregnant and lactating women, as well as relevant available animal and pharmacological data to help

inform prescribing decisions and counselling of women about the use of the product during pregnancy and lactation.

7. Summary

IIVs are not contraindicated for use in pregnancy. The "Indications and Usage" section for these vaccines specifies an age range that includes women of childbearing age. Consequently, the lack of an "Indications and Usage" statement specifically addressing use in pregnant women does not preclude use of these vaccines during pregnancy. Certain countries include information about use of IIV in pregnancy under the "Warnings and Precautions" or "Contraindications" section of labelling. However, this does not reflect a known or suspected safety issue relating to the use of these vaccines during pregnancy but rather a precautionary approach taken by certain NRAs. Programmatic recommendations (such as those from SAGE and some NITAGs) for use of IIVs during pregnancy are consistent with labelling.

8. Authors and acknowledgements

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