FOR DISCUSSION

How may the risk-benefit balance of maternal immunization be best taken into account?

SAGE has long recognized the need for maternal immunization to be better supported whenever it is the best – or the only – strategy to effectively protect mothers and neonates. The GACVS recent review articulates what is known and not known about risks (or lack of risk) from various specific vaccines and substantiates confidence of lack of associated risk with inactivated products. This review is by definition limited to assessing the collected evidence, which remains limited as long as vaccines are contra-indicated during pregnancy.

The following elements may have to be discussed in addition to the vaccine-specific GACVS review.

- Pregnant women have traditionally been excluded from biomedical research because of the lack of knowledge about the potential risks of drugs or vaccines in population perceived as vulnerable. The fear of litigation and the limited expected financial benefits (small market size) has led the pharmaceutical industry to generally deny the enrollment of pregnant women into clinical trials. Consequently, the regulatory files leading to licensing do generally not include information on pregnant women, postponing their acquisition to slow and complex post-marketing surveillance activities or to investigator-driven trials of limited size.

- The same precautionary attitude leads regulatory authorities to exclude pregnant women from the populations to whom drugs or vaccines may be given: “in the absence of data, formulation X should not be given to pregnant women”. Consequently, the use of drugs/vaccines in pregnant or lactating women is traditionally off-label.

- This off-label status creates uncertainties among vaccine recipients and health-care workers about the possibility of using the drug or vaccine. For example, despite a WHO recommendation for off-label use during the roll-out of meningococcal A vaccines in Burkina Faso and neighboring countries, vaccine uptake ended-up being substantially lower among pregnant women than in the rest of the eligible population. Another example is pertussis immunization during pregnancy, recommended in a growing number of countries, despite no vaccine being approved for this use.

However:

- Pregnant women, compared to both the general population and also non-pregnant women of similar age, are at equal or in some cases at increased risk of mortality and serious morbidity from vaccine preventable diseases.

- The early life period, *in utero* or early after birth, is associated with risks of vaccine-preventable diseases which may only be avoided by immunizing pregnant women (tetanus, influenza, pertussis, etc.).

- Decades of vaccine use and a growing number of studies have shown the safety of traditional non-live vaccines (e.g. tetanus or influenza) during pregnancy. To date, not a single licensed non-live vaccine formulation has been associated with enhanced risks of adverse outcome for the

mother, the fetus or the child. Although live attenuated viral vaccines (e.g. measles, rubella or even yellow fever vaccines) or novel adjuvanted vaccines (e.g. squalene-based vaccines used during the H1N1/09 pandemic) have not shown evidence of harm, their pathogenic profile is theoretically higher.

- The enhanced understanding of the mode of action of non-live vaccines (mild transient inflammation and antigen-specific immune activation) provides the biological bases which supports the safety of vaccines in pregnant women. The likelihood that similar non-live vaccines (e.g. dTpa compared to T) would eventually be shown to cause harm if used during pregnancy is thus extremely small.

- The immunomodulatory condition that prevails during pregnancy (minor decrease of cell mediated immunity) does not prevent pregnant women from raising protective vaccine responses providing a direct benefit for them and their fetus or child.

- Waiting for post-marketing surveillance data or investigators-driven trials to provide sufficient high-quality data to result into the licensing of a given vaccine for use in pregnant or lactating women deprives this population, and their offspring, of beneficial effects during many years or decades.

- The current communication by health authorities that vaccines should in general not be used in pregnant women (with a few exceptions such as tetanus or influenza vaccines) generates the wrong message that vaccines may cause harm, and thus markedly reduces their acceptance by physicians and women.

Thus, the current assessment of the risk-benefit balance of maternal immunization is not optimal.

Which strategies could SAGE consider?

- **A traditional approach restricted to vaccine-specific evaluations and recommendations.** The current strategy of collecting vaccine-specific data (mostly from post-marketing studies) is in accordance with the ”doing nothing unless proven safe” principle. It could be considered as the only way to go.

- **The introduction of class-specific evaluations and recommendations.** SAGE could encourage vaccines to be classified among generic groups *(e.g. protein-based vaccines, polysaccharide or conjugated vaccines, vaccines including novel adjuvants, live-attenuated vaccines)* and the degree of confidence on lack of expected risk or possibility of risk be specified by such categories. This would generate permissive or non-permissive recommendations, which would accelerate the recommendation process for the “expected-as-safe” vaccines. A landscape assessment of which novel vaccines (live products, adjuvants, chimeric products, other novel vaccines) may eventually have to be given during pregnancy could be encouraged to include a risk assessment early in the process and thus avoid continuing having important new vaccines but no information about their potential risks in pregnancy.

- **A better consideration of the expected benefits in the evaluations and recommendations.** Although postponing immunization to the post-partum period may be an optimal risk-benefit assessment in certain situations, it becomes inappropriate if the risk of exposure during pregnancy is high (outbreaks, high disease incidence). The risk of missed opportunities, if immunizations are only provided during campaigns, could also be considered. SAGE could recommend that the risks of not immunizing pregnant women be included in the recommendation process.

- **A strengthening of data collection for maternal immunization safety.** SAGE could recommend reinforcing the greater use of registries or other strategies likely to accelerate data collection.

- **The inclusion into the preparation of each immunization trial or program a formal analysis of the expected benefits-risks of maternal immunization instead of automatically excluding pregnant women**. SAGE could recommend to WHO and its partners to include into each new immunization trials or programs a formal analysis of the expected benefit/risks of a priori excluding pregnant women. This evaluation could be supported by a class-specific approach.

- **The recommendation to include new elements (class-specific approach, expected population benefits, etc.) in the WHO prequalification and other regulatory approval processes**. SAGE could recommend this issue to be brought to the International Conference of Drug Regulatory Agencies (ICDRA) and to approach major agencies such as FDA and EMA for possible ways forward. Similarly to pediatric medicines, which required regulators worldwide to take action for studies of medicines in children to be undertaken, some process may be needed.

- **The encouragement of NITAGs and national authorities to actively support maternal immunization,** e.g. with vaccines considered as safe based on class-specific evaluations.

- **The strengthening of communication** on the safety of maternal immunization, when recommended, to reach as many health authorities, physicians and women as possible.

- **Other strategies to be defined.**