WHO INFLUENZA VACCINE RECOMMENDATION

Strategic Advisory Group of Experts (SAGE) on Immunization
SAGE Working Group on Influenza Vaccine and Immunization
## Evidence Evaluation: Conceptual Matrix

**Key Issue**

<table>
<thead>
<tr>
<th>Burden of Disease</th>
<th>Children (&lt;5 years) (&lt;2 years)</th>
<th>Elderly</th>
<th>Pregnant Women</th>
<th>High-Risk Groups</th>
<th>Health Care workers</th>
</tr>
</thead>
</table>

**Vaccine Performance** *(efficacy, effectiveness, impact, safety)*

- What data exist?
- What data are needed?
- What are the gaps?
- What infrastructure or technology could address these issues in the future?
### Assessment of Influenza Risk and Influenza Vaccine Characteristics in Various Risk Groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Feasibility of Delivery</th>
<th>Disease Severity</th>
<th>Vaccine Effectiveness</th>
<th>Indirect Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Healthcare workers</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Children, 2-5</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Children, &lt; 2</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Elderly</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Underlying Health Conditions</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
5 recommended priority groups for countries using or considering introduction of seasonal influenza vaccination.

- Pregnant women highest priority group.
- 4 other priority groups (in no order of priority) are:
  - Health-care workers;
  - Children under 5 (particularly 6-23 months);
  - Elderly;
  - Underlying health conditions.
SAGE recommendations for influenza vaccination (2012)

- Countries with existing influenza vaccination programmes targeting any of these groups (e.g. the elderly to meet WHA 56.19 resolution of 75% coverage by 2010) should continue to do so and should consider incorporating immunization of pregnant women into such programmes.

- Countries should decide individually how they prioritize and develop coverage goals for these groups based on burden of disease, cost-effectiveness, feasibility and other appropriate considerations.
The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach has been adopted by WHO.

GRADE tables that rate the quality of evidence have been produced for influenza vaccine in support of recommendation.
Quality of evidence rating versus vaccine recommendation development

- **Evidence** is rated using GRADE scale based upon analysis of component studies. (e.g. level 4: …very confident that the true effect lies close to that of the estimate of effect on health outcome to level 01: … very little confidence in the estimate of the effect on the health outcome)

- **Evidence** rating helps to inform whether or not a recommendation should be made.

- **Recommendations** are product of data, evaluation of their quality, discussion and deliberation, i.e. other factors are considered in addition to the scientific evidence base

- Strength of **recommendations** refers to the extent to which we can be confident that desirable vaccine effects outweigh undesirable effects.
**Pregnant women, maternal outcome**

**Question:** *Is inactivated influenza vaccine versus no intervention or non-influenza vaccine in pregnant women effective to prevent influenza infection and severe outcomes of infection in pregnant women?*

**GRADE level:** 2 (confidence is limited)

**Knowledge gaps:**
- Lack of information on vaccine efficacy in pregnant women, impact on laboratory-confirmed influenza not sufficiently studied/reported.
- Differences in effectiveness* between active non-influenza vaccine and other vaccine not obvious.
- Lack of placebo controlled trials (comparator previously used was other non-influenza vaccine).
- Shortage and insufficiencies in sensitivity of rapid detection tests impact on evidence obtained from previous studies.

*outcome was clinical visits for respiratory illness with fever
Pregnant women, infant outcome

**Question:** *Is inactivated influenza vaccine versus no intervention or non-influenza vaccine in pregnant women effective to prevent influenza infection and severe outcomes of infection in infants below 6 months of age?*

**GRADE level:** 4 (Confidence is high.)

**Knowledge gaps:**
- Efficacy against laboratory-confirmed influenza in newborns needs to be confirmed in other trials.
- Efficacy needs to be shown from trials that use placebo instead of other non-influenza vaccine as comparator.
- Observational studies require proper reporting of outcomes and appropriate control groups (e.g. not hospitalized children which may bias the effectiveness outcomes).
Infants 6 months to 2 years of age

**Question:** Is inactivated influenza vaccine versus placebo or control vaccine effective to prevent influenza infection in children aged 6 months to 2 years of age?

**GRADE level:** 3 (Confidence is moderate.)

**Knowledge gaps:**
- Lack of efficacy and effectiveness data by infant age-group, small study size in previous trials.
- Lack of efficacy assessment by matched/unmatched strains and by product used.
- Limitations in reporting, lack of standard reporting parameter and less knowledge on their interchangability (efficacy versus effectiveness, PCR-/ laboratory-/ culture-proven influenza).
- Heterogeneity particularly to be addressed in observational studies (variety of follow-up times and ILI case-definitions).
- The role of adjuvants in TIV used in the infant age-group versus non-adjuvanted.
Question: Is inactivated influenza vaccine versus placebo or no intervention or non-influenza vaccine effective to prevent influenza infection in children aged 2 to below 6 years?

GRADE level: 3 (Confidence is moderate.)

Knowledge gaps:
- Lack of efficacy and effectiveness data for 2 to below six year age-group, mostly all age-groups below 6 years of age or all child ages.
- Variation in control groups in trials (placebo, no intervention, etc), which makes it difficult to compare results.
- Bias in some of the existing trials (e.g. allocation concealment, selective reporting).
Elderly aged 65 and above

**Question:** *Is matched, inactivated influenza vaccine versus placebo effective to prevent influenza infection in individuals aged 65+?*

**GRADE level:** 1 (Confidence is low)

**Knowledge gaps:**
- Heterogeneity of age-grouping, epidemiological settings and outcome measured, follow-up times, interventions and rarely stratified results
- Health status of elderly not adjusted (i.e. elderly with chronic diseases and healthy elderly aggregated)
- Limited assessment of baseline imbalance in systematic differences and of external validity, power calculations to detect effect modification by age not routinely done in RCTs
- Selection bias in observational data from differential uptake of vaccination (due to e.g. socio-economic conditions, anxiety or health status)
Individuals with comorbidity - asthma

**Question:** *Is inactivated influenza vaccine versus placebo effective to prevent influenza-related asthma exacerbations in patients with asthma?*

**GRADE level:** 1 (Confidence is low)

**Knowledge gaps:**
- Limited data available to assess benefits of influenza vaccine in asthmatic patients, and only for children
- Limited data available to assess harms of influenza vaccination in asthmatic patients and descriptive or numerical reporting
- Numerous non-standardized primary and secondary outcome measures, e.g. number of asthma exacerbations due to influenza, duration and severity of influenza-related asthma, symptom scores, hospital admissions, pneumonia etc.
- Issues related to late and early outcome measures
- Certain levels of indirectness due to age-group studied and lack of assessment of other respiratory virus associated asthmatic exacerbations
Individuals with comorbidity - HIV

Question: *Is inactivated influenza vaccine versus placebo effective to prevent influenza infection in individuals living with HIV/AIDS?*

GRADE level: 1 (Confidence is low)

Knowledge gaps:
- Risk of high loss to follow-up in this target group
- Low attack rates and low number of observed events - insufficiently powered trials
- Selection criteria for comparison group varied (e.g. HIV positive versus negative individuals, HIV positive vaccinated versus HIV positive non-vaccinated, ART-naïve versus ART-stable)
- Heterogeneity across studies in terms of setting, country, and regarding median/mean CD4+ cell counts of study participants.
- Interplay between change in ART and vaccine effects not fully understood
- Potential role of factors related to HIV-infection (e.g. CD4+ cell count, HIV-RNA load) to be confirmed
**Health care worker**

**Question:** *Is influenza vaccine versus placebo or non-influenza vaccine in health care worker effective to prevent influenza infection of health care worker themselves?*

**GRADE level:** 4 (Confidence is high)

**Knowledge gaps:**
- Not all existing trial use the same outcome and different definitions for ILI are used
- Impacts of secondary prevention (e.g. prevention of nosocomial infection in patients) are not studied
Health care worker and elderly

**Question:** *Is influenza vaccine versus no intervention in health care worker effective to prevent influenza morbidity and mortality in residents of long term care facilities for the elderly?*

**GRADE level:** 1 (Confidence is low)

**Knowledge gaps:**
- Unspecific outcomes such as all cause mortality used in studies and are potentially influenced by other pathogens
- Lack of serological data from HCW may not allow causal attribution
- Risk of bias in RCTs identified due to selection, power and incompleteness
Question: Is seasonal inactivated influenza vaccine versus non-influenza vaccine in pregnant women safe in regard to pregnancy outcomes for the mother and the neonate?

GRADE level: 2 (Confidence is limited)

Knowledge gaps:
- Limited safety assessment in studies (not primarily safety assessment trials)
- No clear definitions on safety outcomes, relatedness and severity of AE in trials
- Not placebo-controlled
- Vaccination in late trimesters, insufficient data for early pregnancy (1st trimester)
- Lack of power analysis to detect rare but severe adverse events
- Observational safety studies prone to bias (lack of causality assessment)
- Factors such as obstetric complications may have impacted on outcomes and increase the possibility for residual confounding
LAIV, children 2 to < 6 years of age

Question: *Is live attenuated influenza vaccine (LAIV) versus placebo or no intervention effective to prevent influenza infection in children aged 2 to below 6 years?*

**GRADE level:** 2 (Confidence is limited)

**Knowledge gaps:**
- Lack of efficacy and effectiveness data for 2 to <6 years age-group, mostly all age-groups below 6 years of age or all childhood ages.
- Limited direct comparisons between LAIV and TIV in this age-group and variations in control groups in trials (placebo, no intervention)
- Bias in some of the existing trials (e.g. randomization, selective reporting).
Challenges for 2012 recommendation - 1

Vaccine performance:

- Safety of different vaccines (TIV, adjuvanted TIV and LAIV) in pregnancy and other risk groups – GAVCS
  - Safety at different trimesters of pregnancy
  - Safety in persons with underlying health conditions
- Model on impact of immunization in LMIC for:
  - pregnant women and newborns
  - the elderly
  - Children less than 5
- Duration of protection (e.g. in maternal immunization) – review and studies
Challenges for 2012 recommendation - 2

Policy development and enhancement

- Development of guidance on prioritization of targeted risk group and coverage goals with key recommendations on maternal and elderly influenza immunization for LMIC
- Encourage countries to invest in surveillance and disease burden analysis to inform policy development
- Regional policy development/enhancement workshop on seasonal influenza vaccine
- Development of criteria for success; continuous evaluation and monitoring tools for implementation
Challenges for 2012 recommendation - 3

Vaccine supply:

- Country specific supply-demand analysis (pre-purchase agreements?)
- Discussion with manufacturers on:
  - Year-round supply of vaccines for immunization of pregnant women
  - Shelf-life of vaccines

Regulatory issues:

- Labeling and package insert
Challenges for 2012 recommendation - 4

Vaccine communication:

- Building communication strategies for immunization to address specific targeted groups
- Mapping of factors relating to influenza vaccination reluctance, development of evidence based messages to address factor on vaccine reluctance and evaluate the effectiveness of such messages
- Building consensus with medical and professional organization (societies and colleges for obstetricians) for recommendation / position statements
Challenges for 2012 recommendation - 5

Economic analysis:

- Cost-effectiveness analysis of maternal and other immunization strategies (children & elderly) for seasonal influenza

- Modeling for cost-effectiveness for influenza vaccine in maternal immunization programs for LMIC

Implementation:

- Strategy for vaccination implementation – e.g. maternal tetanus program, EPI or others