1. Welcome, Background, and Role of Working Group

Elizabeth Miller, the chair of the SAGE Working Group (WG) on Influenza Vaccines and Immunization, welcomed everyone to the first meeting and noted the range of accomplished experts. The purpose of this introductory meeting was to orient the WG members, to discuss WGs and their role with SAGE, to define the scope of the objectives, and to develop an approach to meet the objectives of the WG.

Objectives of the Working Group:
1. Prepare for a SAGE evidence-based review and updating of WHO recommendations on the use of seasonal influenza vaccine (e.g. priority target groups) with a particular focus on low and middle-income countries and with a view to update the 2005 WHO influenza vaccine position papers.
2. Prepare for a SAGE discussion on coverage goals for seasonal influenza vaccination to be proposed to the WHA to update the coverage goals contained in the 2003 resolution.
3. Identify essential gaps in evidence that may impede SAGE's ability to update the recommendations on the use of influenza vaccines and propose coverage targets.
4. Provide advice about pandemic vaccine preparedness.

The 4th item relates to long term strategic thinking, including the role of vaccines in the broader context of influenza prevention and control approaches. This WG builds on the work of the SAGE H5N1 WG (to complete its work at the November 2010 SAGE meeting) and the SAGE H1N1 WG (already completed); issues of seasonal and pandemic vaccines will now be reviewed and deliberated upon by the current WG on Influenza Vaccines and Immunization. As with all SAGE WGs, WGs are resources for SAGE to help review the evidence and facilitate proposals for recommendations to be considered by SAGE. There may be utility in some interaction with other advisory committees (such as the Global Advisory Committee on Vaccine Safety (GACVS) and the Quantitative Immunization and Vaccine Related Research (QUIVER) committee). Declarations of interest are very important for WG members and the Secretariat should be notified if WG members' situations change. It is proposed that the WG present their proposals for recommendations regarding the vaccine position paper to SAGE at the November 2011 SAGE meeting.

One of the WG's key tasks is to assist with the updating of the WHO influenza vaccine position paper. In addition to updating the recommendations from the 2005 influenza vaccine position paper, the WG is asked to provide input into which recommendations should be formally

1 http://www.who.int/entity/immunization/wer8033influenza_August2005_position_paper.pdf
graded. The WG may request additional scientific expertise as needed (for example, from a member of QUIVER regarding cost-effectiveness analyses).

2. Review of activities previously conducted by the SAGE H1N1 and H5N1 WGs

The H1N1 WG was established in May 2009 and concluded its work in April 2010. The H1N1 WG's main focus was to provide SAGE and the DG with proposed recommendations for immunizing populations against the H1N1 pandemic, including defining target groups for immunization based on the goals of the country and considering H1N1 vaccine safety, number of doses needed, and co-administration of seasonal and pandemic vaccine.

Although strain selection is a technical process based on virologic and antigenic criteria, there are occasions where policy implications may impact these decisions. For example, during the H1N1 pandemic policy considerations were important for decisions about vaccine formulations and valency.

There are a number of areas where the recent experience with H1N1 may provide additional data for the WG's consideration. Important areas warranting further review include seasonality and timing of influenza transmission around the world, regional and climatic variability, duration of protection, shelf-life of vaccines (particularly for pandemic vaccines), burden of disease data, impact of adjuvanted vaccines on duration of protection, and follow up of individuals who received the H1N1 vaccine but do not receive seasonal influenza vaccines on a regular basis. Guidance on when to switch from seasonal vaccine production to pandemic vaccine production would also be useful.

The H5N1 WG was established in April 2008 and will make its final report to SAGE in November 2010. The main focus of the H5N1 WG was to propose recommendations on the details of the H5N1 stockpile, including size and utilization. The H5N1 WG recommended the WHO establish a stockpile of 150 million doses for two purposes: rapid containment and vaccination of essential personnel. Later discussions questioned the validity and feasibility of a rapid containment approach, and the H5N1 WG will propose to SAGE that the entire stockpile should be dedicated to vaccinate essential personnel. As a result, pandemic vaccine may be stored in bulk (prolonging the shelf life) but will need to be transferred to a fill/finish facility prior to use. Currently the stockpile is still virtual although there have been commitments made from GSK and Sanofi Pasteur. The H5N1 WG also considered inter-pandemic vaccination strategies and the evidence base for containment vs. population protection.

3. Update on the report to the WHA as a request from WHA 56.19

In May 2011 the World Health Assembly (WHA) will receive the Secretariat report on the progress made by WHO and Member States from May 2003 through September 2010 for prevention and control of influenza (there will be a separate document about pandemic influenza compiled by the International Health Regulations (IHR) Committee). This document and the associated background materials may be useful for the WG moving forward on their own tasks. Seventy-four countries have seasonal influenza programs, none of which are in the African or South-East Asian regions. The WHO Public health research agenda for influenza (2009) is now in the implementation phase and a toolbox is being created for developing countries to assist with studies on disease burden, statistical programming, and other areas. The importance of understanding the impact of secondary bacterial infections was emphasized and some work is being done on this through the research agenda.
The burden of disease data being collected as part of this activity and the associated systematic review should be available at the end of 2010. WG members provided suggestions for improving the document and the Secretariat is revising accordingly. The Secretariat also requested input from the WG on the role of vaccines in the greater influenza prevention and control effort.

4. **Review of information available and gaps on influenza disease burden**

A review of information available and the gaps on influenza disease burden was presented, with a focus on the developing world. It is difficult to measure the burden of influenza, in part due to the wide variation in the estimated numbers of deaths from season to season, for which an important factor is circulating influenza virus types and subtypes. Available data suggests different severity of disease based on the strain. A meta-analysis is being conducted by the WHO Global Influenza Program in collaboration with the University of Edinburgh. The review is taking published and unpublished data from a number of sites worldwide; preliminary results suggest there is a greater burden of influenza acute lower respiratory infections in developing countries compared to industrialized countries, and a draft report should be available for the WG to review at the end of the year. Climate is clearly an important consideration in disease transmission, as seen by H1N1 influenza transmission patterns in the northern temperate regions, the tropics, and the southern temperate regions. There was no clear pattern of transmission evident in the tropical regions, in contrast to the temperate regions for which seasonality patterns were closely aligned. The need for surveillance, including background rates, standardization of surveillance methods and case definitions, and international data sharing, was emphasized. It was noted that the review found a significant proportion of bacterial infections associated with influenza pneumonia.

Much of the available data focuses on childhood disease, although this is only a piece of the true burden of influenza; it was suggested the lack of focus on adults should be highlighted as a gap. Furthermore, many surveillance studies use PCR to detect influenza virus, but this approach may miss those cases when an individual becomes PCR-negative but goes on to have complicated disease. The measurement of attributable burden of disease (e.g. due to secondary bacterial infections) versus the single cause (influenza only) burden is a major diagnostic and methodological challenge. In developing countries there are no studies based on ICD codes that can evaluate clinical outcomes. It was suggested that there should be more prospective sero-epidemiology studies to evaluate the burden of influenza. The WG's assessment of the burden of disease may be a key issue warranting application of formal GRADE scoring of the quality of scientific evidence.

Issues regarding influenza seasonality were raised. Much of the data currently available in developing countries are for H1N1, but the seasonality of seasonal influenza may be quite different. This was highlighted for India, which has two peaks of transmission (one in the monsoon months and one in the winter) and is correlated with humidity. This transmission pattern has implications for timing of vaccination.

A further challenge is identifying individuals who fall into high risk groups targeted for vaccination. Patient lists used in developed countries do not exist in developing countries, making such individuals harder to identify. Pregnant women, another high risk group, are more easily identified and should be given greater attention as a target group for vaccination. Pregnant women are an accessible group as they already receive tetanus toxoid during
pregnancy. It was suggested that the WG advocate for greater inclusion of pregnant women in future studies. Additional data on this group may be available through the Pregnancy Influenza Project (PIP) study in the spring of 2011 and NIH-sponsored trials. Another potential high risk group identified was children under one year of age. Infants, particularly those in the first few months of life, often present with just fever and are frequently admitted to the hospital to rule out sepsis. Vaccinating pregnant women may be an important strategy to protect both groups, mother and infant. Another special population to consider are HIV-infected individuals, with attention given to their therapy status. Questions regarding pneumococcal conjugate vaccines and detection of pneumonia attributable to influenza were raised.

The WG put forth a number of key questions for deliberation in the coming months. Regarding recommendations for influenza vaccine use, two main questions were identified: 1) how strongly should the WG recommend influenza vaccination? and 2) for which populations? Another related question is what are the key barriers that are preventing a more forthright recommendation for influenza vaccination outside of the industrialized world? That is to say, what data are the WG missing or have not yet considered? Examples of issues proposed included burden of disease, cost-effectiveness, realistic implementation, vaccine availability, financing, and the ability to reach the target. It was suggested that risk factor considerations (e.g. increased complications and severe illness due to influenza infection among pregnant women) likely do not differ between developed and developing countries and knowledge acquired from the industrialized world can be largely generalizable. There will be several specific issues to consider, such as malnutrition, obesity, and impact of other infectious diseases (TB, Malaria, HIV, etc).

Issues of prioritization for vaccines and populations to receive influenza vaccines were discussed. Countries may have a difficult time deciding to include influenza vaccines in the national immunization program when resources are limited and other vaccines, such as for rotavirus and pneumococcal, are also being considered. It was stated that countries will need to have a sense of how much influenza will decrease morbidity and mortality compared to other vaccine preventable diseases. An important component of this is understanding vaccine effectiveness in the tropics, which is currently not well understood. There was a discussion on the possibility of doing a demonstration study in a developing country with a clear seasonality (possibly South Africa) to assess vaccine impact in different risk groups.

5. Influenza disease burden in China

There are a number of challenges for evaluating disease burden in developing countries. These include underestimates of the true influenza burden, limited laboratory diagnostic capacity, differences in health utilization and medical seeking behaviour, and the variable seasonality of influenza. Robust virological surveillance data and high quality, representative, long-term viral registration mortality data are needed. However, a recent study found influenza to have a significant impact on influenza-associated mortality in various regions of China, with the elderly population most affected. A review of Chinese supply and capacity revealed that current supply is able to vaccinate approximately 1.9% of the Chinese population, while 43% of the population currently falls into a high risk group recommended for annual vaccination. Competing priorities with other vaccines as well as the significant cost are major obstacles. Annual administration of seasonal influenza vaccine would cost $5.7 billion for vaccination and delivery, not to mention the cost of increasing production capacity to meet the needs of the population. A major consideration from this assessment is if vaccination efforts could become more targeted to increase feasibility and cost-effectiveness (not assessed so far).
6. Influenza in Africa - What do we know?

There is limited information on influenza in Africa and there are limited resources to address the needs. Because of the variability in data across African study sites, it is not possible to conclude what the true burden of influenza disease actually is across the continent and it is unclear to what extent influenza vaccination should be a priority in these countries. Complicating factors in Africa include dynamics of transmission, high pneumonia mortality in children, conflict in some settings, and factors that increase vulnerability to influenza (such as malnutrition, HIV/AIDS, co-infections, and limited access to health care). The first meeting of the Africa Flu Alliance was held in June 2010 as a forum for discussion and information sharing. At the meeting challenges were identified and a road map of activities and interventions was developed to strengthen data collection, national capacity, and patient care. The importance of publishing data generated from the African surveillance activities was emphasized, and activities are under way to facilitate publication of studies.

Due to the lack of data for evidence-based recommendations in some contexts, the WG may make conditional recommendations to permit for regional differences. The challenge of vaccine prioritization for countries with limited resources was highlighted. Lack of data on disease burden makes this very challenging, particularly in developing countries. However, there is some data (e.g. from Madagascar) that could be extrapolated to other contexts. The question of whether there are regional differences in risk groups was raised.

7. Update on 2010 seasonal influenza vaccine coverage in WHO Member States

A survey is in progress to identify seasonal influenza vaccine national policies and coverage levels in WHO Member States. The same survey was first conducted in 2007 and is being redone in 2010. In 2007, among those countries that responded to the survey, about one half had a routine influenza vaccination program. Collection is on-going for the 2010 survey and data will hopefully be available by the end of 2010. The results of the current survey may inform WHA targets for influenza vaccination, if a target is deemed a useful measure of success. WG members indicated there are other data available in the interim that would be informative. The Joint Reporting Form co-administered by WHO and UNICEF collects immunization data from the Member States, including nationally recommended schedules for influenza vaccination, on an annual basis.

8. Seasonal influenza vaccination uptake in the Americas: strategies and successes

PAHO's technical advisory group (TAG) issued recommendations for seasonal influenza vaccination in 2004 and 2006. They have found positive support for TAG recommendations, which included strengthening surveillance systems and strong vaccination policies. Of those countries with national policies, there is variability in national recommendations. For example, of the 35 countries and territories with policies for influenza vaccination in 2008, 33 recommended vaccination of the elderly, 32 recommended vaccination of health care workers, and 7 recommended vaccination of pregnant women. Many countries met WHA targets for vaccination of the elderly. There may be valuable lessons learned for what approaches worked in which target groups in PAHO countries. The WG requested briefings from a few PAHO countries about their experiences (countries suggested included Argentina, Brazil, Chile, Costa Rica, El Salvador, and Mexico). The WG is interested in hearing about why and how each country chose their target groups, what the implementation strategy was, what coverage was
achieved, and what impact data are available. The WG was also interested in the methodologies used to estimate vaccination coverage, whether cost-effectiveness analysis had been done in the countries, and whether any impact assessments are being done.

9. Discussion of 2010 work plan of the SAGE WG on Influenza Vaccines and Immunization

The WG discussed the importance of both updating the vaccine position paper and providing strategic guidance on the long term future of influenza vaccines and immunization programs. The WG has the dual function of assessing the current evidence of influenza burden of disease and seasonal vaccination opportunities, as well as defining the innovation needs in order to increase the feasibility of seasonal influenza vaccination in lower-middle income countries. In that context, the innovation leap coming from live attenuated influenza vaccine (LAIV) technology and adjuvanted vaccines needs to be carefully assessed.

The WG Terms of Reference may need to be adjusted to appropriately capture this objective. Recommendations that fall outside the scope of the vaccine position paper may be included in the SAGE reports. It was stressed that this is an opportune time for a global vision for influenza vaccines and should be capitalized upon by the WG.

Some challenges the WG will have to discuss include the lack of disease burden data in developing countries, supply issues and how to prioritize vaccine among risk groups when there is insufficient quantity to meet the demand, questions around vaccine efficacy, and how to evaluate cost-effectiveness when there is a lack of data (despite this being a critical consideration for countries when making policy decisions). The existing coverage targets require a critical review.

The WG identified 3 main themes for structuring future WG deliberations:

1. Burden of disease
2. Vaccine efficacy/performance of the vaccine and cost effectiveness
3. Operational issues

A potential 4th that was suggested was supply/production. To begin identifying data gaps and support needs, the WG agreed to develop a matrix of the key themes listed above stratified by target groups.

The WG requested a teleconference be scheduled towards the end of this year to make concrete decisions about the plan of action, the matrix, and future meetings. The WG agreed a second face-to-face meeting would be needed, perhaps after some of the data currently being collected are ready (such as the meta-analysis). The suggestion was made to have two in-person meetings, one focusing on the burden of disease and practical issues, and the other on safety and effectiveness. The WG requested the development of an activity plan with questions to address, deliverables, and tentative timelines. WHO staff will meet to discuss internal next steps and staffing needs.
Appendix 1. List of Participants

Working Group Members

Professor Jon Abramson
Dr William Ampofo
Dr Joseph Bressee
Dr Janet Englund
Dr Randeep Guleria
Dr Yu Hongjie
Professor Elizabeth Miller, Chair
Professor David Salisbury
Professor Barry Schoub
Professor Claire-Anne Siegrist

Unable to attend

Dr Michael Pfleiderer

WHO Secretariat

Mrs Kanokporn Coninx
Dr Philippe Duclos
Dr Joachim Hombach
Dr Marie-Paule Kieny
Dr Mike McNeil
Dr Anthony Mounts (Day 2)
Dr Cuauthémoc Ruiz-Matus (Day 2, by phone)
Dr Nahoko Shindo
Dr John Tam
Dr Claudia Vivas Torrealba
Ms Kirsten Vannice (served as rapporteur)
Appendix 2. Summary of key points identified

**General**
- How strongly should the WG recommend seasonal influenza, and for whom?
  - What data are needed to do this?
  - Is a stronger recommendation for children (or any other group) warranted, or might it be in the future?
- What are the key barriers to a forthright recommendation outside of the industrialized world?
  - Hierarchy of issues (e.g. burden of disease, cost-effectiveness, realistic implementation, vaccine availability, financing, ability to reach target)
- This WG’s recommendations may be similar to the current recommendations, but the format may be quite different
- There are examples of successful influenza vaccination programs and lessons from these experiences should be built upon

**Special Populations**
- Are risk factor data generalizable across settings (e.g. pregnant women)?
- Some high-risk populations are harder to target in developing countries, where those populations are not easily identifiable (no patient lists)
- **Pregnant women**
  - This group should receive more attention as a target group for vaccination
  - The current vaccine position paper recommendation (Influenza vaccination in pregnancy is considered safe and is recommended for all pregnant women during the influenza season) would benefit from more clarity
  - This is an accessible group (already receiving tetanus toxoid)
  - Review of data suggests this mortality among pregnant women may be reduced with proper management
  - Double impact (protect both mother and infant)
- **Children under 1 year**
- **Obese/morbidly obese**

**Secondary bacterial infections**
- What is the true impact and how can it be measured?
- Challenges with “attributable” mortality

**Role of Cost-Effectiveness**
- Challenging to do, but WG should not be limited by it
- Interaction with QUIVER

**Grading of the Evidence**
- Adjustments to GRADE are evolving
- What key questions should be graded?
  - Grading of burden of disease data

**Role of LAIV**

**Adjuvants**
- Long-term effectiveness in vaccinees with adjuvanted vs. non-adjuvanted H1N1 vaccine

**Shelf life (particularly for pandemic vaccines)**
Importance of a wholistic approach for preventing and controlling influenza in developing countries (not only vaccines, and other measures may be more appropriate depending on the context/goals, e.g. chasing after transmission)

• WG can help define the role of vaccines

Role of climate/humidity/altitude in disease transmission

• Impact on timing of vaccination

Much focus on children, not adults

Target coverage levels

• The ability of the WG to recommend a target level of influenza vaccination coverage may depend on the strategy (population based vs. health care workers)

Seasonal vs pandemic vaccine production

• Should there be a recommendation to cease production of seasonal vaccine in the event of a pandemic?
  o Financial implications for who will compensate industry

Process of integrating strain selection with policy recommendations

• Should it be independent of SAGE or can it be harmonized?
• Although a technical process based on virologic and antigenic criteria, there are policy implications (e.g. tetravalent and bivalent vaccines, adding pandemic strain to seasonal to slowly increase protection)

Influenza vaccine as a priority compared to other vaccines

Scale of production

• To have sufficient vaccine for target populations, will need significant increase in capacity

Programmatic Needs

• Surveillance: background data, standardization of surveillance methods and case definition, international sharing of data, etc.
• Laboratory capacity

Measuring success

• If success is measured by coverage in a certain group but the country decides to target a different group, rates of success could be misleading

Prioritization

• To do nor not?
• Approach?

Sparse data in many regions, particularly tropical

• Burden of disease
• Vaccine efficacy
• Cost-effectiveness
• Indirect effects (herd immunity)
• Best time to vaccinate (and duration of antibodies)
• Variability, even within one country (e.g. China)
  o Implications for strain selection
• Different strains cause different severity of illness—must be monitored over time
• Reliance on PCR means missing cases, especially in countries without surveillance using ICD codes, for example
• Much data that will be available are for H1N1, but there may be important differences with seasonal influenza
• Disease prevented by pneumococcal vaccination vs. influenza vaccination
• Need for sero-epidemiology studies