1. Welcome and opening remarks:

Joachim Hombach welcomed meeting participants and introduced the WHO secretariat to the SAGE Working Group on Influenza Vaccines and Immunization (WG). John Tam was introduced as the new WG focal point from the secretariat. Elizabeth Miller, the chair, welcomed everyone to the second meeting of the WG, and outlined the agenda to be covered over the next two days.

2. Review of previous meeting, action items and needed reports/statements for SAGE

The WG were reminded of its Terms of Reference (ToR) which were as follows:

- 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 (LMI) in order to update the 2005 WHO influenza vaccine position paper.
- 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.
- 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.
- Provide advice about pandemic vaccine preparedness.

Where appropriate, advice from other advisory committees such as GACVS and QUIVER would be sought on specific issues.

A summary of the key recommendations from the Nov 2010 SAGE meeting was also presented. Those relevant to the WG’s deliberations were as follows:

1. The draft conceptual framework that would provide the structure for the position paper was approved by SAGE with the recommendation that health care workers should be added as a key target group

2. SAGE endorsed the WG’s suggestion that as part of its activities it should develop an influenza research agenda
3. With the dissolution of the Influenza pandemic influenza H5N1 WG, SAGE recommended that the Influenza WG re-consider options for the nature, deployment and storage of the remaining doses of H5N1 vaccine pledged for the WHO stockpile, taking account of logistic and other lessons learned from deployment of the H1N1 (2009) pandemic vaccine stockpile.

The expectations for this meeting were as follows:

- Review details of the conceptual matrix and identify information gaps and needed research
- Review disease burden in the key target groups
- Consider the options for the H5N1 pandemic stockpile and if possible submit draft recommendations for consideration at the April 2011 SAGE.
- Consider the implications of the recent data on the possible link between Pandemrix H1N1 vaccine and narcolepsy for future recommendations about the use of oil-in-water adjuvanted vaccines
- Agree timelines and future WG meetings for completion of the WG’s remit

It was noted that while key WG recommendations would need to be subject to the GRADE system of evidence, this method was not appropriate for statements about the burden of disease due to influenza. Furthermore since the GRADE system in its current form was not always appropriate for evaluating the strength of the evidence for vaccine policy recommendations (which need to take account of factors such as herd immunity that could only be assessed in observational post-licensure studies) WHO was reconsidering how the GRADE system could be adapted for SAGE vaccine recommendations. The WG would be kept informed of these deliberations by the SAGE secretariat.

3. **Update on activities of the WHO Global Influenza Programme**

The WG received an update from Dr. Nahoko Shindo of the WHO Global Influenza Programme on its recent report to the WHA in relation to existing resolutions that impacted on influenza. She presented an overview of current burden of disease data collated by the Global Influenza Programme (GIP), with special emphasis on the LMI countries. The WG received a tabled report from GIP of a systematic literature review on seasonal influenza disease burden and a summary presentation of a meta-analysis on global burden of influenza in children, together with an analysis on risk factors for severe pandemic 2009 influenza infection. Data from LMI countries are currently insufficient to allow most to prioritize strategies for influenza prevention and control over other interventions.

The WG was reminded that the WHA resolution on the prevention and treatment of pneumonia (WHA63.24) was also relevant to its deliberations. Currently, the resolution focuses on bacterial pneumonia and emphasizes treatment in the form of Integrated Management of Childhood Illnesses and use of PCV and Hib vaccines. However, the resolution recognizes the impact of the 2009 influenza pandemic and mentions respiratory syncytial virus and seasonal influenza as the most common non-bacterial cause of pneumonia. Thus the outcome of the Influenza WG’s discussions may influence WHO’s pneumonia control strategies.

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Resolution WHA 56.19, that identifies the elderly as the highest risk group for influenza-associated severe illness and mortality, was discussed by the WG. In relation to recommendations that would have relevance for LMI countries it was noted that the age structure of the population in resource poor countries is different to that in high income countries where the elderly formed a relatively larger proportion of the population. In LMI countries, influenza in the very young (<2 years of age) is potentially more important in terms of overall population burden of disease than influenza in the elderly. This is because young children are at higher risk of influenza-associated hospitalization (e.g. pneumonia) and comprise a larger proportion of the population than in high income countries. Given the positive impact of maternal and childhood influenza immunization on influenza-related morbidity in young children that has been demonstrated in recent studies and the high proportion of the population comprising young children and pregnant women in developing countries, the WG agreed that it was important to provide clear recommendations to SAGE for these groups.

4. Presentation of the conceptual matrix on WG activities

The conceptual matrix that will frame the work of the WG was presented (See matrix in appendix). It included:

Identification of 5 key population groups:

1. children < 2 years,
2. elderly,
3. pregnant women,
4. high risk groups
5. health care workers (HCWs).

For each of these population groups the following data was required

- burden of disease
- vaccine performance and cost effectiveness
- operational issues affecting vaccine delivery

Questions to populate the matrix:

- What data exists?
- What additional data are needed?
- What are the gaps?
- What infrastructure or technology could address these issues in the future?
- What information is being collected and when will they become available?
- What additional activity is needed to identify and/or compile the data?
Discussion on needed research associated with the conceptual matrix to inform development of a Research Agenda

Key issues:

- Health care workers were considered a priority group; a key issue to tackle was how to address their reluctance to receive vaccine. The importance of getting evidence on the benefit of influenza immunization in this group was stressed. The concept of vaccinating not only for the protection of HCWs but also as a duty of care for protection of vulnerable patients was considered to have special value. Review of evidence (using GRADE criteria) of the need for and benefits of vaccinating HCWs with a strong policy statement was needed.
- There is also an information gap on disease burden and vaccine effectiveness for children < 2 years. Of these children < 6 months of age formed a special group as they could be protected by maternal immunization.
- Burden of disease data for the remaining groups (elderly, pregnant women and other high risk groups) were considered adequate. Use of the H1N1 (2009) experience for assessing the increased risk in these groups was considered appropriate for extrapolation to seasonal influenza.

Burden of disease: The need for better burden of disease data on children <2 years of age who would be a potential target group for seasonal influenza vaccine was identified as a high priority. CDC is currently conducting an extensive review of the global burden of influenza disease (see below) and agreed to assess whether the data collated for this review could be re-analysed to identify the burden of influenza in <6 months and 6 months to <2 years to help inform the WG’s deliberations.

Vaccine performance (efficacy, effectiveness, safety) for different vaccines i.e. Live attenuated influenza vaccine (LAIV, traditional trivalent inactivated vaccines, and inactivated vaccines with new adjuvants): Ideally effectiveness data by vaccine type in the 5 key population groups would be required in order to define which type of vaccine would be best in which group. However, it was unlikely that the necessary data would exist for all groups and, where considered clinically appropriate, extrapolations from the available data would need to be made.

Vaccine effectiveness and cost effectiveness: The Secretariat may commission a systematic literature review to assess the available data and if there is sufficient, to initiate a meta-analysis of vaccine effectiveness and cost-effectiveness particularly for LMI countries. This should include review of the available evidence on the newly licensed LAIV for seasonal influenza. The potential value of oil-in-water adjuvanted vaccines should be considered.

Operational issues: These would differ depending on the type of vaccine, age and population group under consideration.

It was agreed that an influenza vaccination programme targeted at pregnant women and infants was the most feasible to implement in LMI countries given the existing vaccination programmes for these groups. School age children were considered a potentially important target group for influenza vaccination, especially as they may have a key role in transmission as suggested by studies in developed countries. However, the applicability of these findings for LMI countries would require knowledge of mixing patterns, e.g. how social networks are established and how children gather in different settings, which would vary with the local setting. A study had been sponsored by IVR to define contact matrices in developing countries.
Communication issues were considered important but not the main focus of the WG. Evaluating the evidence on the impact of different communication strategies will be helpful. Learning from the experience of regions and countries would also be of value, especially when considering targeting specific risk groups like pregnant women and HCWs.

Issues on vaccine production capacity were also discussed. The report from the Open-Ended Working Group of Member States on Pandemic Influenza Preparedness: sharing of influenza viruses and access to vaccines and other benefits (OEWG) meeting is expected to provide key information in this regard. There is a need to increase global seasonal influenza vaccine production capacity; for example in China the vaccine production capacity fell substantially short of the number of dose needed to cover the targeted groups. Regulatory issues could be an obstacle in certain countries.

Efficient deployment of seasonal influenza vaccines required better information on seasonality and the circulating strains, especially from countries in tropical areas.

Vaccine stability: There are operational advantages of having a more stable formulation and encouragement for further research needs to be highlighted.

5. Review of disease burden and risk factors for severe disease

In the 2005 influenza vaccine position paper, five priorities groups were recommended to receive influenza vaccination:

- Residents of institutions for elderly people and the disabled,
- Elderly, non-institutionalized individuals with chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies
- All individuals >6 months of age with any of the conditions listed above
- Elderly individuals above a nationally defined age limit, irrespective of other risk factors
- Other groups defined on the basis of national data and capacities, such as contacts of high-risk people, pregnant women, health-care workers and others with key functions in society, as well as children 6-23 months of age.

These groups were defined based largely on data from industrialized countries. The WG were presented with new data on the epidemiology, risk factors and burden of disease by the GIP and CDC. The data presented focused on newer studies from LMI countries and from ongoing work with influenza disease burden models. Data from the 2009-10 H1N1 pandemic were highlighted in many of the discussions.

**Disease burden:**

One information gap that has made the development of global influenza vaccine policy difficult is valid estimates of global or regional disease burden. Countries with robust data on disease burden, mostly high-income countries, have used the data to create policy and to implement vaccine programs, while most other countries where data are few haven’t had the necessary information for decisions. The WG were presented with the preliminary results of two models of global disease burden – one for children under 5 years and one for global pandemic mortality in all ages.
An ongoing collaboration between many sites worldwide and chaired by researchers at the University of Edinburgh has estimated the total < 5 years influenza-associated respiratory disease burden. They have estimated that influenza accounts for 13% of all acute lower respiratory illnesses among this age group and 7% of all hospitalized ALRIs. This disease burden indicates that influenza accounts for greater numbers of ALRI than other vaccine preventable diseases, pneumococcal and HiB-associated disease, but fewer than RSV. They concluded that that there was evidence of 1-3 fold increases in the rate of ALRI and severe ALRI in developing country settings compared with developed country settings. Though the relative increase in developing countries seemed higher for ALRI this may be due differences in the surveillance method, with ALRI being ascertained by active rather than passive methods. The risk of both outcomes was higher in children under 2 years than those 2-5 years.

A model created by US CDC has estimated the global burden of disease associated with pandemic influenza, which the WG considered contained lessons for seasonal influenza-associated disease burden. While the overall estimates of pandemic-associated deaths ranged widely from 100,000 - 578,000, the model found that more than half the deaths were among persons living in Africa and Southeast Asia. These results confirmed other studies that have demonstrated greater pandemic burdens in developing countries and an association between income level and lower pandemic mortality rates from earlier pandemics.

**Identification of high risk groups**

**Age:** Data presented from GIP and CDC also focused on recent data on groups at high-risk for severe influenza or influenza-associated complications. Relevant data were presented both from seasonal and H1N1 pandemic studies.

While actual rates of influenza-associated deaths vary greatly from year-to-year and study to study, elderly persons are clearly at higher risk of death from influenza. New data from limited LMI countries confirm that the risk of influenza-associated death among elderly persons in developing countries (e.g. South Africa) may be several times higher than among similarly aged persons in high-income countries.

Children in LMI countries also appear to have higher rates of hospitalizations associated with influenza, though where access to health care is poor hospitalisation rates may be lower than in high income countries. In LMI countries the hospitalisation rates in children are similar to those in the elderly while mortality is much lower. And while data are available to estimate relative burden of influenza among children (see models above), it was acknowledged by the WG that a better understanding of the effects of influenza on the youngest children (<2 years) and those <6 months would be helpful for developing policy for vaccination. It was noted that studies may have underestimated pediatric disease rates. Because of the differences in rates of elderly and pediatric outcomes in limited studies, the WG indicated that extrapolation of rates of severe outcomes from high-income to LMI countries would be problematic.

The relatively high burden of influenza in low resource settings might be due to age structure differences; higher proportion of pregnant women in the population; limited access to health care; malnutrition; increased secondary bacterial infections that are not well treated; lower pneumococcal/influenza vaccination rates, different co-morbidities; and untreated co-morbidities.
Continued efforts to understand these factors and how they might effect vaccine strategies were called for.

It was also stressed that estimating possible impacts of an influenza vaccine program must account for the age distribution in the population and the effectiveness of vaccine in the populations. So while elderly persons may be at highest risk of death from influenza, it is conceivable that greater disease reduction might be achieved by focusing vaccination programs on young children or other groups. Additional work needs to be done in modelling the possible effects of various immunization strategies.

**Underlying health conditions:** Data were also presented regarding groups at high risk of severe influenza due to underlying condition. It was agreed that the effect of underlying clinical conditions was likely to be similar in high income and LMI countries. Data clearly indicated that pregnant women were at particularly high risk of severe complication and deaths from influenza (including seasonal and pandemic, and possibly avian influenza H5N1). And while pregnancy alone is a risk factor, the presence of co-morbidities (obesity, asthma, diabetes, etc) conferred even higher risk.

Also, abundant data exist that underlying chronic medical conditions (e.g. lung disease, including asthma, heart disease, endocrine disorders, neurological diseases etc.) confer higher risk of severe disease and death associated with influenza. It was concluded, however, that more data were needed on the effect of chronic infections such as HIV/AIDS and TB in LMI countries, where these conditions were less likely to be treated than in high income countries. Finally, data from the pandemic on 2009-10 clearly demonstrated that indigenous populations were are at high risk of complications from influenza.

**Summary**

Several conclusions could reasonably be drawn from the discussions:

- Acknowledging the limitations of the data, influenza hospitalization and death rates are likely higher in LMI settings than in high-income settings. A substantial proportion of pandemic mortality may have occurred in these settings.
- Some data from high-income countries, such as identification of likely high risk groups, can reasonably be applied to LMI countries where such data are sparse. However, one can’t reliably extrapolate age-specific outcome rates from high-income to LMI settings. Ongoing efforts to model disease burden in LMI countries based on data from these settings will be important to establish appropriate vaccine policies.
- Pregnant women and young children are at high risk of hospitalizations, and depending on demographic characteristics of a population in LMI countries, may represent important targets for prevention through influenza vaccination.
- Significant gaps remain to fully understand the burden and risk groups for severe influenza in LMI countries. Better data on the effects of underlying illnesses common in LMI countries (e.g. TB and HIV), of malnutrition, of local bacterial pathogens, and of seasonality will be important to design and evaluate optimal prevention programs.
- The WG supports continued work to fill these gaps.
Discussion on knowledge gaps and future actions for disease burden analysis in key target groups

The University of Edinburgh global burden of disease review and other papers on the pandemic disease burden estimates will be published over the next few months (timeline not specified). It was recognised that, while these publications will be very helpful, there will inevitably be a lack of reliable data on the effect of age and co-morbidities on mortality in LMI countries. However, extrapolation of disease severity and burden from high to low income countries using both seasonal and pandemic H1N1 (2009) influenza should be possible for the following risk conditions:

- pregnant women
- people with underlying diseases
- AIDS/immunocompromised

Co-morbidity: incidence/mortality multiplier will be higher in developing countries since control of disease is poorer in such countries. It would be helpful if the available data on mortality could be presented by age (children <2 years, adults and elderly) and risk group and not just geographically.

In addition, any information on the following questions also can be helpful:

- Is there an increase in pneumococcal infections during influenza seasons?
- Is there a significant burden of influenza illness that may not present with fever and thus not be picked up in surveillance based on influenza like illness for which fever is a necessary symptom?
- How do socioeconomic factors affect severity and mortality?

6. Preliminary findings: 2010 Survey for the global mapping on the use of seasonal influenza vaccine II

The main source of information for this presentation was data from the WHO 2010 Global Influenza Vaccine Survey that is currently taking place. Other sources of information considered included the survey undertaken by the Vaccine European New Integrated Collaboration Effort (VENICE) project in 2008 across 27 EU Member States, Norway and Iceland, the research article published in 2009 in BMC on the Expansion of seasonal influenza vaccination in the Americas, the study done in Sep 2010 by the International Federation of Pharmaceutical Manufacturers, and the Join Reporting Form (JRF) between UNICEF and WHO.

Member States with seasonal influenza in national immunization schedule varies from region to region. Findings were described as follow:

- In AFR according to the JRF, only Algeria, Mauritius, and South Africa recommend vaccination for specific target groups.
- In AMR 91% of the countries have annual seasonal influenza vaccination as part of the national immunization, and Dominica is expected to introduce it soon.
- In EMR, 33% of the countries have an annual seasonal influenza vaccination and one country (Iraq) is expected to do so by 2012.
- In EUR, information from 27 EU countries showed that all of them recommend seasonal influenza vaccination.
- In SEAR, only Thailand recently introduced seasonal influenza vaccination.
• In WPR, 6 countries already have seasonal influenza as part of national immunization schedule and by 2012 Singapore and the Philippines are expected to include it.

It is worth noting that some countries offer vaccination in the private sector even though it is not part of the national immunization schedule.

The following target groups are recommended to be vaccinated according to the WHO survey data available by the date of this presentation:
• In AMR 83% of the countries are recommending vaccination among children, 53% of the countries in the region recommend vaccination in adults, 94% of the countries recommend to vaccinate the elderly, and 70% of the countries recommend to vaccinate at risk groups.
• In EUR, data included from the VENICE survey indicated that 85% of the countries recommend vaccinating the elderly, and 100% of the countries recommend vaccinating at risk groups.
• Globally, 90% of the countries consider chronic pulmonary and cardiovascular disease when recommending vaccination for at risk groups.
• Pregnant women are recommended to get vaccine in around 45% of the countries.
• As for essential personnel, the majority of the countries considered health care workers, lab workers and field workers that investigate outbreaks as the main groups to be vaccinated.
• Other groups such as travelers, military and other sectors were also considered but in a minor proportion.

Data were presented as percentage of countries provided recommendations to the total countries that responded to the survey. WG members suggested further examination of the survey methods and how these data were calculated.

Another aspect that the survey is trying to elucidate is the vaccination coverage rates by target groups. Unfortunately, it cannot be calculated at this stage, due to the fact that many countries do not register the number of people being vaccinated by groups. For the regions that are able to calculate coverage, data is inconsistent and is difficult to provide generalizations.

Seasonal influenza vaccine is administered in both public and private sector. When administered in the public sector, the vaccine is free of charge in the majority of the cases.

The WHA 56.19 set the goal of achieving 75% influenza vaccination coverage among the elderly in those Member States having a national influenza vaccination programme targeting the elderly. According to survey results, this goal is difficult to achieve. By the date of this report, 13 countries in AMR, five in WPR and only one in EUR have achieved this goal.

The source of seasonal influenza vaccine varies from region to region, for example, in PAHO it is mainly through the bulk purchase mechanism. In EMRO vaccine is acquired through a combination between bulk purchase and direct purchase and in WPRO it comes from UNICEF, direct purchase and donations.

According to the IFPMA, the total number of doses distributed worldwide has increased by 72% rising from 262 million doses in 2004 to 449 million in 2009. Growth occurred in all of the six WHO regions, although distribution in the Americas peaked in 2007 and subsequently fell by approximately
6%. The combined WHO provision of seasonal influenza vaccines in 157 countries showed that Europe and Americas regions accounted for 75 - 80% of the total doses distributed each year.

Regarding H5N1 pandemic vaccine, the percentage of countries potentially requesting H5N1 vaccine doses from WHO stockpile would be around 85%. The essential personnel that would require H5N1 vaccination includes HCWs, lab workers, field workers investigating animal and human outbreaks, security forces and other sectors. The percentage of H5N1 vaccine doses required for essential personnel in the different regions varies from 7% in AMRO/PAHO, 6% in SEARO and 17% in EMRO. However, these percentages should be considered cautiously as it only represents small portion of the regional population. In those countries that may potentially require more doses, the list of essential personnel proposed includes a larger part of the total population.

EURO data from JRF will be checked regarding non EU countries. The WHO survey will be shared with the group to identify which data might be useful for further analysis. Draft report from the 2010 WHO survey for global mapping use of seasonal influenza vaccine will be available by the end of April 2011.

7. Discussions on pandemic H5N1 stockpile

Background

The following background information was provided to the WG in a verbal briefing from Dr. Marie-Paule Kieny

- In May 2007 The World Health Assembly recommended to the DG of WHO that an international stockpile of H5N1 vaccine should be established.
- In November 2007, after reviewing available safety and immunogenicity data on H5N1 vaccines, the WHO SAGE recommended that WHO establish a stockpile of around 150 million doses.
- Based on scenarios explored by two mathematical models, the advice from SAGE was to reserve 50 million doses for an immediate containment operation in the countries with sustained community spread with the objective of aborting or delaying the nascent pandemic.
- The remaining 100 million doses were to be deployed to low and middle income countries in amounts proportional to their population size (sufficient for ~1% of the population, assuming a two dose schedule) to protect public health by helping to maintain essential services. Health care workers were identified as a key target group.
- Two manufacturers responded with pledges to donate vaccine to the WHO stockpile. GSK pledged 50 million doses and Sanofi-Pasteur 60 million.
- With Gates Foundation funding an external company, Oliver Wyman, was commissioned to consider logistic and financial implications of these recommendations. Considerable cost implications were associated with maintaining a physical stockpile, particularly in filled doses as would be required for mounting a rapid containment operation. Other options of having a virtual H5N1 stockpile were also explored.
- The analysis of lessons learnt from the H1N1 pandemic promoted a review of the SAGE recommendations on deployment of the stockpile, its composition and storage in the light of the following:
  - Containment strategies designed to shut down a nascent pandemic for which 50 million doses had been reserved were no longer considered feasible.
• Experience with the unexpected emergence of H1N1 highlighted the risk with commitment to a physical stockpile of H5N1 i.e. all pledged vaccine potentially being the wrong strain.
• GSK and Sanofi in recognition of their previous H5N1 pledge agreed to "convert" this pledge into H1N1 pandemic vaccine. Subsequently, these pledges were increased to 60 million from GSK and 100 million from Sanofi Pasteur. Of these potential 160 M doses of H1N1 vaccine, some 40 million doses were used by WHO for deployment in low and middle income countries. This reduced the remaining number of pledged pandemic vaccine doses to around 120 million.
• As a result of the experience in switching their pledged H5N1 doses to a different strain, manufacturers indicated greater flexibility in relation to their original H5N1 stockpile commitment.
  – Under the option of committing to a virtual rather than a physical stockpile they would be able to switch production to the relevant pandemic strain when it emerged and not be restrained by their pledge to provide H5N1 pandemic vaccine (as exemplified by their response to the H1N1 pandemic).
  – If a physical stockpile was required then this would have to be H5N1 (as this is the only subtype whose production is currently supported by a few paying customers) but could be stored by the manufacturer

In the light of points above the Influenza Working Group was asked to re-consider options for the nature, deployment and storage of the remaining 120 doses of pledged vaccine.

**WG discussion and draft recommendations**

There was initial discussion on whether the existing SAGE recommendations on the pre-pandemic use of available H5N1 vaccine should be reconsidered, given the emerging information on safety and efficacy of the H1N1 pandemic vaccine and the recognition that pandemic vaccine manufactured once the next pandemic was declared would likely be deployed too late to prevent a substantial proportion of cases (as with H1N1 vaccine).

• The current SAGE recommendation did not recommend pre-pandemic use of H5N1 vaccine, with the exception of laboratory staff handling the virus and animal workers who may be exposed to highly pathogenic avian viruses. However, there was provision for review of this recommendation if circumstances or knowledge changed. It was suggested in discussion by members of the WG that further consideration be given to the wider pre-pandemic use of H5N1 vaccine with the intention of priming key target populations to allow boosting with a single dose should an H5N1 pandemic emerge with a different H5 virus.
• After discussion it was agreed that there was currently no new information or risk assessment that would merit a change in the existing SAGE recommendation regarding pre-pandemic use of H5N1 vaccine. Despite the generally encouraging safety profile of the various H1N1 vaccines used in 2009/10, narcolepsy had emerged as a potential safety signal with one vaccine and was still under investigation. Also in view of the H1N1 experience there was now more caution in assuming that the next pandemic would be H5N1. In the absence of a quantifiable risk of H5N1 infection, the risk benefit of more widespread vaccination remained unfavourable at the present time. In addition, the key target group of health-care workers is notoriously reluctant to influenza immunization, predicting very poor acceptance.
• However, in line with the SAGE recommendation this would be kept under view, and revisited should circumstances change. The potential availability of new seasonal vaccines
containing putative pandemic antigens that could be used for priming at the same time as providing annual protection against seasonal influenza strains was noted.

- In relation to the use of the pledged 110 million doses of pandemic vaccine, the WG considered three main options:
  - To generate a physical H5N1 stockpile, stored largely as bulk, possibly held by the manufacturer. The issue of replenishment would arise when the stockpile became out of date and all pledged doses would be committed to H5N1. There are also issues (cost, location etc.) relating to the identification and qualification of an independent fill-finish facility that can rapidly response to the emergence of a H5 pandemic.
  - To keep all the vaccine as a virtual stockpile, only specifying the strain when the pandemic emerged. This was the least costly option and least risky in terms of expending the pledged doses on the wrong virus. To ensure as timely delivery as possible, manufacturers would be asked to reserve 10% of the filled doses produced each week under contract for countries buying their own vaccine for the WHO stockpile.
  - As b above but to have a small quantity of the pledged doses (say 1% of the total, ~1 million) as a physical H5N1 vaccine stockpile in filled vials that could be immediately deployed as part of a local H5N1 outbreak control measure in the event of enhanced person to person spread in one or more countries. This use was not the same as the containment policy as the intention was to provide protection for those at immediate risk (such as those needed to maintain essential health services), not for the interruption of transmission of a nascent pandemic.

- Option c was favoured as it would provide reassurance to countries without their own H5N1 stockpile that in the event of an outbreak with a highly pathogenic H5N1 virus, some protection could be offered to those in the exposed local population. Although the physical stockpile would need replenishing at regular intervals, it would not materially deplete the remaining number of pledged doses in the virtual stockpile.

- A number of practical questions followed from option c.
  - Could this small physical stockpile be held by the manufacture?
  - If the manufacturer was producing H5N1 vaccine to provide for countries compiling their own stockpiles in filled doses, could the WHO stockpile for immediate deployment be cycled within that ongoing stock?
  - Countries wishing to be able to access this physical stockpile would need to develop an implementation plan to ensure that it could be rapidly deployment as part of an outbreak control measure.
  - WHO would need to have criteria and plans for the rapid despatch of H5N1 vaccine to an outbreak area and criteria for release in response to a county’s request.
  - In deciding on the number of doses in this small stockpile it would be helpful to know how storage costs (if not borne by the manufacturer) relate to the number of doses held – say over the range 100,000 to 2 million) and to draft potential scenario of stockpile use.
  - WHO should ensure that all existing licensed pandemic or pre-pandemic H5N1 vaccines, and those in the physical stockpile, are pre-qualified. Since vaccine in the virtual stockpile could be of any strain e.g. H9, H7, then pre-qualification of a generic vaccine from a manufacturer based on the EMA “mock up” dossier principle should be pursued.
In summary, the WG concluded that the virtual stockpile option with a small physical stockpile of filled doses of H5N1 vaccine for outbreak control would provide maximum flexibility, minimize costs especially those involved with replenishment, obviate the risk of expending the pledged doses on the wrong vaccine and simplify the logistics of storage. WHO should ensure that it has procedures in place to facilitate the earliest possible receipt and deployment of pandemic strain vaccine to the low and middle income countries who would be dependent on the WHO stockpile in the event of another pandemic, and that procedures are in place for rapid delivery and utilization of the physical H5N1 stockpile released for outbreak control. The Chair of the WG will present the recommendations for consideration by SAGE at its meeting in April, 2011.

8. Information on adjuvanted H1N1 vaccine and narcolepsy

The WG was provided with an update on the position with respect to the reported association between narcolepsy and Pandemrix as this may have bearing on any draft recommendations on the use of seasonal influenza vaccines containing an oil in water adjuvant. The WG was informed that:

- Following widespread use of vaccines against influenza (H1N1) 2009, cases of narcolepsy, especially in children and adolescents, have been reported from at least 12 countries. Rates reported from Sweden, Finland and Iceland have been notably higher than those from other countries.
- Studies are ongoing to determine if the apparent increased risk of narcolepsy reported in Sweden is higher in vaccinated persons.
- In Finland, the risk of developing narcolepsy among those vaccinated with Pandemrix aged between 4 and 19 years is about nine times greater than those unvaccinated in the same age group, corresponding to a risk of about 1 case of narcolepsy per 12,000 vaccinated in this age group. The increased risk has not been seen in younger or older age groups in Finland. 22/22 cases of narcolepsy tested so far in Finland has the (HLA) DQB1*0602 genotype.
- The only pandemic vaccine used in Finland was Pandemrix, an adjuvanted influenza (H1N1) 2009 monovalent vaccine manufactured by GlaxoSmithKline. Finnish authorities consider it probable that Pandemrix vaccine was a contributing factor to the observed increase in narcolepsy, and has called for further investigation of other co-factors that may be associated with the increased risk.

The WG noted the GACVS risk assessment that concluded:

- An increased risk of narcolepsy has not been observed in association with the use of any vaccines whether against influenza or other diseases in the past. Pandemrix vaccine was used in 47 countries worldwide during the 2009-2010, and it does not appear that narcolepsy following vaccination against pandemic influenza is a general worldwide phenomenon, and this complicates interpretation of the findings in Finland.
- Any increased risk of narcolepsy currently appears to be restricted to the months following vaccination and by age group and country. GACVS agrees that further investigation is warranted concerning narcolepsy and vaccination against influenza (H1N1) 2009 with Pandemrix and other pandemic H1N1 vaccines and GACVS will continue monitoring the situation closely.

The WG also noted that there was no change to the current WHO position on the use of pandemic influenza vaccines which was that countries should continue vaccinating against H1N1 to immunize
persons at risk of severe disease from H1N1, using monovalent vaccines including Pandemrix, if trivalent seasonal vaccine is not available. It also noted that no regulatory action had been taken by the European Medicines Evaluation Agency and that Pandemrix remains on the list of WHO-prequalified vaccines.

The WG noted that further information on the association between narcolepsy and receipt of Pandemrix vaccine would not be available until later in the year and that any recommendations about the use of oil in water ajuvanted seasonal influenza vaccines that the WG might include it is position paper would have to await the outcome of these pending studies and to be reported by GACVS.

9. Summary of action points and closure

- **Understanding of severity for informing recommendations**: Revisit again the evidence on burden of disease when pending papers become available. These papers on evidence will be shared by emails. An assessment containing all information available will be provided by the secretariat. Joe Breese will help the secretariat in putting it together.
- **Vaccine effectiveness**: Some consolidated evidence relevant to the topic needs to be scrutinized and should be made available for next meeting. It will include studies on efficacy and effectiveness. Cost effectiveness studies will be limited to seasonal influenza vaccine. For young children effectiveness on seasonal and pandemic vaccines will likely be similar. This issue will be discussed in the next face to face meeting.
- **For both of the above items, particular emphasis should be put on the collection of disease burden data relevant to children <2 years of age**.
- **Next meetings to be held**:
  a. Preparatory teleconference before next face to face meeting to be held in July 2011
  b. Face to face meeting: by end of August of beginning of September 2011. This meeting will be in preparation for the meeting to be held the second week of November. Two other meetings that might generate important information for the group will be held between June and July, the first one on maternal immunization and later the GAP-II meeting.
- **What to report back to SAGE in April?**
  a. Disease burden in the key target groups
  b. Conceptual matrix, needed research and further timelines and work plan
  c. Feedback on the discussions on the nature and use of the pandemic vaccine stockpile
  d. Information needed with respect to future policy recommendations for all influenza vaccines
- **Minutes of the meeting will be available by end of Feb together with the complete set of slides**
- **As documents (papers, reports, studies, etc) become available the will be circulated among the Influenza WG members.**
- **SharePoint**: A virtual space will be created in order to share all relevant documents, i.e. minutes, slide presentations and relevant information/publications.
• For SAGE report: include the minutes of this meeting. Other relevant reports such as the burden of disease paper, or documents needed in yellow book need to be ready by March 16th.
• Narcolepsy and Pandemrix: just as part of the report for this group. Not extra action needs to be taken.
Appendix 1 Agenda

Appendix 2 Conceptual matrix

Appendix 3 List of participants

Working group members:
Professor Jon S. Abramson
Dr William Ampofo (Apologies)
Dr Joseph S. Bresee
Dr Janet Englund
Dr Randeep Guleria
Dr Yu Hongjie (Apologies)
Professor Elizabeth Miller (Chair)
Dr Michael Pfleiderer
Professor Art Reingold
Professor David Salisbury
Professor Barry D. Schoub,
Professor Claire-Anne Siegrist

WHO Secretariat
Dr Philippe Duclos
Dr Joachim Hombach
Dr Marie-Paule Kieny
Dr Pem Namgyal
Dr Cuauthemoc Ruiz-Matus
Dr Nahoko Shindo
Dr John S. Tam
Dr Claudia Vivas Torrealba (rapporteur)
Dr David Wood
AGENDA

Day 1, Monday, 14 February 2011, Room C202

09:00 - 09:10 Welcome and opening remarks
Chair: Liz Miller
Rapporteur: Claudia Vivas

09:10 - 09:30 Review of previous meeting, action items and needed reports/statements for SAGE
Philippe Duclos

09:30 - 09:45 Update on the report to the WHA as a request from WHA63.19
Nahoko Shindo

09:45 - 10:00 Presentation of the conceptual matrix
John Tam

10:00 - 10:45 Discussion on needed research associated with the conceptual matrix and the development of a Research Agenda (SAGE recommendation)
Led: Chair

10:45 - 11:15 Refreshment Break

11:15 - 12:30 Discussion on future timelines and work plans associated with the conceptual matrix
Led: Chair

12:30 - 13:30 Lunch Break

13:30 - 14:00 Review of disease severity and burden in key target groups
Nahoko Shindo

14:00 - 14:30 Review of global disease burden
Marc-Alain Widdowson (TC)

14:30 - 15:30 Discussion on knowledge gaps and future actions for disease burden analysis in key target groups
Led: Joe Bresee

15:30 - 16:00 Refreshment Break

16:00 - 16:30 Discussion on report to SAGE on disease burden analysis
Led: Chair

16:30 - 16:50 Preliminary findings: 2009 Survey for the global mapping on the use of seasonal influenza vaccine II
Claudia Vivas

16:50 - 17:00 Summary of day 1 activities
John Tam

17:30 - 19:30 Cocktail
<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Lead</th>
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<tbody>
<tr>
<td>08:30 - 09:00</td>
<td>Background and WHO conceptual directions for H5N1 stockpile</td>
<td>TBD</td>
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<tr>
<td>09:00 - 11:00</td>
<td>Review the needed information and strategy in relation with stockpile and the use of pandemic vaccines</td>
<td>Led: Chair</td>
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<td>11:00 - 11:30</td>
<td>Refreshment Break</td>
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<tr>
<td>11:30 - 12:15</td>
<td>H1N1 vaccine safety review</td>
<td>David Wood</td>
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<td>12:15 - 12:45</td>
<td>Discussions on 2011 workplan of the SAGE WG and Summary report to SAGE on 5 April 2011</td>
<td>Chair</td>
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<tr>
<td>12:45 - 13:00</td>
<td>Summary of action points and closure</td>
<td>Chair</td>
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### SAGE Working Group on Influenza Vaccine and Immunization: Conceptual Matrix for information required for recommendations

**Questions to populate the matrix**
- What data exists? At this stage as discussed, what would be needed is not an exhaustive list but indication of availability of data and critical pieces of info.
- What data are needed?
- What are the gaps?
- What infrastructure or technology could address these issues in the future?
- What information is being collected and when will it become available?
- What activity is needed to identify and/or compile the data?

<table>
<thead>
<tr>
<th>Key Issue</th>
<th>Children (&lt; 2 years?)</th>
<th>Elderly</th>
<th>Pregnant Women</th>
<th>High Risk Groups</th>
<th>Health care workers</th>
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| **Burden of Disease** | 1. (GIP) Covered as a part of overall BoD in Sub-Saharan Africa lit review. Manuscript submitted to Lancet ID.  
2. (GIP) Pediatric BoD lit review done in collaboration with Edinburgh University. Manuscript due submission to peer-reviewed journal. Includes data from high & middle-income tropical countries.  
3. (EPA)* Pediatric ILI burden in primary care in 6 seasons: 47-83% due to influenza.  
| **Vaccine Performance (efficacy, effectiveness, safety) broken down for different vaccines i.e. LAIV, traditional, adjuvanted** | Extensive data on efficacy of seasonal influenza in infants and children exists from clinical trials for TIV, LAIV and adjuvanted killed influenza vaccine. Requires systematic lit review on efficacy for different age groups (such as <2, <5 etc.) | Limited data exist on TIV for the elderly and efficacy is less than that for children. Systematic lit review required to understand knowledge gaps especially for LAIV and adjuvanted vaccines. | Data may exist for pandemic H1N1 vaccine and being made available gradually but little is known for seasonal vaccine. Requires systematic lit review. | (GIP) Literature review of efficacy of vaccination for severe immunocompromised underway, report 28Feb11.  
Lit review required for other risk groups such as patients with chronic diseases. | (GIP) Literature review of efficacy of vaccination of HCW in preventing nosocomial infection and spread in patients underway, report 28Feb11. |
| **Cost-effectiveness** | Extensive lit review required for cost effectiveness analysis for all age and risk groups. Information gaps likely exists and additional cost effectiveness studies will be required for specific groups. | | | | |
**Operational Issues**

<table>
<thead>
<tr>
<th>H5N1 Vaccine:</th>
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<tbody>
<tr>
<td>1. Clarity H5 vaccine stockpile strategy (virtual vs. physical) and selection criteria for acceptance of vaccines into the stockpile</td>
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<tr>
<td>2. Collect information on existing country-specific H5 vaccine pre-purchase plans, stockpiles and expiration dates</td>
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<tr>
<td>3. Planning on the provision for storage, rapid fill and finish facilities for H5 vaccine and adjuvant</td>
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<td>4. Define priority groups for H5 vaccine and estimate size of priority groups identified nationally, regionally and globally</td>
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<td>5. Development of deployment and communication strategies, and initiate ethical discussion for H5 stockpile deployment</td>
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<tr>
<td>6. Identify strategy for rapid detection, assessment and investigation of adverse events</td>
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<tr>
<td>7. Identify methods for assessment of effectiveness when the vaccine is deployed</td>
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<td>8. Monitor research on heterotypic 'priming' (possible use of stockpile in the event that H5 pandemic strain differs from stockpiled H5 vaccine strain)</td>
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<td>9. Monitor research on development of new vaccines for H5 (LAIV etc.)</td>
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<th>Pandemic Vaccine:</th>
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<tr>
<td>1. Review of lessons learnt from pandemic (H1N1) 2009 vaccination activities</td>
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<tr>
<td>2. Review of vaccine deployment/delivery procedures for current H1N1 pandemic vaccine particularly for low income countries</td>
</tr>
<tr>
<td>3. Review of H1 pandemic vaccine effectiveness and cost-effectiveness</td>
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<tr>
<th>Seasonal Vaccine:</th>
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<tr>
<td>1. Survey of seasonal vaccine policy and pandemic vaccine preparedness for high, medium and low income countries.</td>
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<tr>
<td>2. Review seasonal vaccine production capacity in high vs. mid and low income countries, and coverage goals</td>
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<tr>
<td>3. Regulatory requirements, similarities, differences among high and low income countries</td>
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<tr>
<td>4. Possible harmonization of regulatory requirements among agencies including WHO pre-qualification standards for pandemic and seasonal vaccines among epidemiologically/geographical similar countries</td>
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<td>5. Identify optimal strategies for each of the risk groups for annual vaccination programmes.</td>
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<td>6. Investigate the effect of herd immunity on influenza control</td>
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<tr>
<td>7. Review of data on transmission of influenza within family members and develop strategy on family vaccination programme that include all ages</td>
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<tr>
<td>8. Evaluate studies that examine effective mechanism of communication for increasing the use of influenza vaccine</td>
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<tr>
<td>9. Monitor research that address the correlates of protection against influenza in humans</td>
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<tr>
<td>10. Monitor progress on research associated with needle free vaccination for seasonal influenza.</td>
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<tr>
<td>11. Monitor research on more stable vaccine formulations that require less stringent conditions for storage and delivery</td>
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*EPIA: The European Paediatric Influenza Analysis Project. Eur J Pediatr, 2010*