World Health Organization

2nd MEETING OF THE SAGE WORKING GROUP ON
INFLUENZA VACCINES AND IMMUNIZATION
14-15 February 2011
WHO Geneva

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 influenza SAGE working group focal point from the secretariat. Elizabeth Miller, the chair, welcomed everyone to the second meeting of the WG, and outlined the expected agenda to be covered over the next two days.

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

During this session the WG Terms of Reference (ToR) were presented:

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 paper.
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.

Interaction with other advisory committees such as GACVS and QUIVER is envisaged. The next steps and timelines of the WG were discussed. Activities included the development of an action plan with deliverables and timelines, the development of a conceptual matrix, compilation of data and the proposals for SAGE on updating the vaccine position paper and long-term strategy and innovation.

A summary of the key recommendations from the Nov 2010 SAGE meeting was also presented, including the request on the assessment of utilization of WHO deployed pandemic influenza vaccine, for which data collection is ongoing and available data will be presented in the next SAGE meeting. The revision of lessons learned from H1N1 vaccination activities, and the need for more information on shelf life and other characteristics of the H5N1 pandemic vaccines were identified prior to making additional recommendations on the stockpile of the H5N1 pandemic vaccine. The report from the Influenza WG to SAGE is to include the challenges on programmatic and policy development, manufacturer capacity, surveillance and laboratory capacity, as well as prioritization of target groups for vaccination and epidemiological variability in different regions

of the world. The conceptual matrix was supported by SAGE and in addition, SAGE recommended the development of a research agenda for influenza vaccine as an additional deliverable.

Issues and actions to flag included the possibility of grading the burden of disease. It was indicated that this is not possible at present with the current data available, the SAGE requested feedback from PAHO countries experience in implementation, prioritization of target groups, strategy, coverage and impact.

The expectations for this meeting were presented as follow:

1. Review disease burden in the key target groups
2. Review details of the conceptual matrix and discuss the needed research and future timelines and work plan
3. Review the needed information in relation with the discussions on the H5N1 vaccine stockpile and the use of the pandemic vaccine stockpile
4. Discuss the information needed with respect to future recommendations for all influenza vaccines (particularly adjuvanted vaccines) in light of the GACVS statement on the possible association of narcolepsy and Pandemrix. The format of interaction with GACVS and QUIVER will be defined, since not specific areas of work that might be commissioned to them have been identified.
5. Discuss tentative plans to provide support for a related SAGE discussion at the April 2011 meeting.

3. Update on the report to the WHA as a request from WHA 63.19

All documentation submitted to the Executive Board (EB) was asked to be shortened. The update covered the topics of global alert system, the health impact, the status of influenza vaccination programmes, the global vaccine production capacity , the global pandemic influenza action plan, to increase vaccine supply, the WHO's vaccine stockpile and distribution , the preparedness plan , the research and development activities, coordination with other organizations and antiviral activities.

WHA resolution 63.19 refers to pandemic influenza preparedness, virus sharing and access to vaccines and other benefits. It was reminded that this is a multiagency task, since it involves trade issues, has economical implications and involves intellectual property concerns. The main task of the IHR review committee is to review the pandemic response. EB decision was made to consider these reports and merge them. The report will not be reviewed by the WHA but will be use as part of the discussion. Studies that support the report will be reviewed in a later stage; current papers are not for circulation, they are aimed to go for peer review soon.

Other relevant resolutions involving different WHO clusters such as HSE and FHC were mentioned, specially the one on treatment and prevention of pneumonia that the EB recommended adopting for the 63rd WHA; respiratory syncytial virus was recognized as the most common cause of pneumonia vs. bacterial infection. The resolution WHA 56.19, that identifies the elderly as the highest risk group, was discussed among meeting participants, the importance of young children as a high risk group for pneumonia highlighted the positive impact that maternal and childhood influenza immunization might have if implemented in developing

countries was consider necessary. The group discussed the potential benefit of having a clear recommendation on this regard to SAGE.

4. Presentation of the conceptual matrix

The conceptual matrix that will frame the work of the group was presented. It included: 1) the key issues for children < 2 years, elderly, pregnant women, high risk groups and health care workers (HCWs). 2) The burden of disease 3) vaccine performance 4) cost effectiveness and operational issues. (See matrix in appendix)

Questions to populate the matrix:

- What data exists? (At this stage as discussed, what would be need is not an exhaustive list but indication of availability of data and critical pieces of information)
- 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 they become available?
- What activity is needed to identify and/or compile the data?

5. Discussion on needed research associated with the conceptual matrix and the development of a Research Agenda (SAGE recommendation)

Key issues:
Health care workers were considered a priority group; issues to be tackle were how to address the needs of this group and their reluctance to receive vaccine. The importance of getting data on the effect of influenza immunization in this group was stressed. The concept of vaccinating not only for the protection of HCWs but also on the transmission of influenza to the patients was considered to have special value. Review of evidence with a strong statement was considered needed. There is also an information gap regarding the disease burden and vaccine effectiveness for children < 2 years, especially regarding those < 6 m. Other groups such as the elderly, pregnant women and other high risk groups were agreed as presented.

Burden of disease: taking into account on the time frame and the objectives on promoting influenza seasonal vaccination especially for the high risk groups, it was considered important to understand the disease burden first, the type of research needed to be conducted, further activities may require an extension of timeframe.

Vaccine performance (efficacy, effectiveness, safety) broken down for different vaccines i.e. LAIV, traditional, adjuvant: these studies were considered specific for particular populations; however some information could be generalized such as the protection of infants. The groups convened that recommendations should be based on the best available evidence. It is needed to have clear data on efficacy per age group combined with risk groups, before embarking on effectiveness studies. Studies that define the best vaccine to be used (LAIV, TIV, adjuvanted etc.) in different risk groups by considering the duration and spectrum of protection, vaccine effectiveness and safety.

Vaccine effectiveness and cost effectiveness: considering the availability of data, the secretariat may perform a systematic literature review and if information are adequate, to initiate a meta-analysis of vaccine effectiveness and cost-effectiveness in middle and low income countries.

Operational issues: Many of the issues raised were considered as longer term activities. Acknowledging that this type of information gathering and research need to take place, the WG need to establish priorities on what can and needs to be done within a realistic time frame. Operational strategies might differ depending on age and population groups to be considered, and different topics require different solutions. Aggregated data for children < 2 including those < 6m and pregnant women are considered important. Even though the focus of the Influenza SAGE WG is on seasonal influenza, data on pandemic (H1N1) 2009 is also needed to complement the information.

Regarding school age children, it was considered as an important target group for influenza vaccination. Approach to increase coverage in this age group is dependent on local characteristics, including issues like how social networks are established and how children gather in different settings. Information required to support this initiative include review of data on transmission of influenza within family members. Development of strategies on family vaccination programme to include all ages can be considered. It was mentioned that The University of Minnesota is currently conducting a review on this topic.

Communication issues were considered important but not the main focus of this group. There is no doubt that a better communication strategy is needed for implementing vaccination policies. Evaluating the evidence on the benefit of having good communication strategies will be helpful. Experience from regions and countries will be of value, especially when considering targeting specific risk groups like pregnant women and HCWs.

Issues on vaccine production capacity were also discussed; report from the OEWG meeting is expected to provide key information in this regard. There is a need to increase seasonal influenza production capacity, especially for the southern hemisphere. Regulatory issues could be an obstacle in certain countries; for example, vaccines acquired by countries in the southern hemisphere that are not licensed in the country of origin (from the northern hemisphere). Studies and data on seasonality, strains and herd immunity are needed, especially from countries in tropical areas and the southern hemisphere.

Vaccine stability: Operational advantages of having a more stable formulation, and encourage further research needs to be highlighted.

6. Review of disease severity and burden in key target groups

The 2005 position paper priorities were presented; those were made considering data from industrialized countries and included:

1. Residents of institutions for elderly people and the disabled,
2. Elderly, non-institutionalized individuals with chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies
3. All individuals >6months of age with any of the conditions listed above,
4. Elderly individuals above a nationally defined age limit, irrespective of other risk factors,

5. 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.

When considering the elderly, high income-temperate countries and middle and low income countries were taking into account. It was discussed that if the objective is to prevent severe influenza, the priority group should be the elderly, although not knowing if response to vaccine will be good. Two main descriptions of impact were considered: proportion of deaths, and relative risk of death in different population groups.

Recommendations need to be adapted to countries and will depend on vaccine effectives, therefore a range of vaccination options should be available. Life expectancy rate in developing countries should be considered and estimate burden of disease should be based on population data. Translation into any recommendation will depend on vaccine efficacy. Hospitalization rates in children are similar to the ones in elderly. Overall mortality is substantial for children and it is underestimated.

Adult mortality using example from developing countries such as South Africa, Argentina and Colombia were presented. Mortality rates due to influenza and pneumonia in these countries varied from 8 to 151.9 per 100,0000 in the >65 age group. Another study on the viral aetiology of severe pneumonia among Kenyan infants and children showed that about 6% of pneumonias are caused by Influenza type A. All studies showed high impact that influenza has in developing countries.

In pregnant women, the higher risk of severe complication and deaths from all forms of influenza (seasonal, avian influenza H5N1 and pandemic H1N1) was shown. During the post partum period, studies do not show an increase in complications. Most of women would have influenza before delivering. Pregnancy is a risk factor for severe pandemic H1N1 infection. When considering individuals with co-morbidities, pregnancy alone is considered as a risk factor and is exacerbated by the presence of co-morbidities. Patients are more likely to die of influenza infection if they have other background co-morbidities (i.e. asthma, neurological diseases etc.) More studies are needed related to other chronic infections such as HIV/AIDS and TB.

7. Review of global disease burden

An update on recent and ongoing studies on seasonal influenza, challenges and next steps was presented from US CDC.

When comparing rates of influenza related all cause mortality in different setting, the elderly aged ≥65 years were clearly more affected. Influenza-related excess mortality was shown in the elderly in South Africa (SA) in a study conducted from 1998 to 2005, rates were standardized for comparing SA and the USA and shown to have a higher impact in SA.

Burden of influenza in low resource settings might be due to age structures differences; more pregnant women, low health care access and provision, malnutrition, increased secondary bacterial infections and not well treated, lower pneumococcal/influenza vaccination rates, different co-morbidities, and untreated co-morbidities. Global influenza burden among children

< 5 years shown that in low resource settings there is a possible 3-fold increase in ALRI , a 1.4 times increase risk for severe ALRI and the < 2 y old are at higher risk than 2-4 years old.

Pandemic influenza mortality estimates shown that 32% of all death in Africa, 27% in Southeast Asia and 16% in western Pacific, while the Americas, Europe and the Mediterranean are less affected. An increased mortality worldwide among indigenous groups was also observed. The relative risk on the cumulative incidence of hospitalization; admission to an intensive care unit or death from pandemic (H1N1) 2009 in pregnant and indigenous Australians was also higher. A strong association of mortality with per capita income by country was reported with an estimate of 10% increase in income equating to 10% decrease in mortality.

The fluctuation of influenza incidence in different West African countries was presented; it varied from country to country and from one period of the year to another. The challenges in burden estimation were summarized as follow: measuring mortality in the absence of vital statistics, non-respiratory diseases outcomes, deaths occur at home in poor rural settings, and modeling excess mortality in settings without clear seasonality. Other questions raised were: How and why do attack rates vary from year to year and place to place and difficulties in identifying risk factors associated with severe influenza disease that can help target vaccination.

The next steps that the US CDC group will take will be:

- Determining global burden of influenza
- Proportional model to validate rate-based approach for children
- Regional estimations of excess mortality using vital statistics gathered in certain regions
- Work on individual country burden estimates hospitalizations combining Demographic Health Survey and surveillance data
- Population-based sites generating rate data
- Re-calibrate surveillance systems to ensure collecting valid data on risk factors and young infants

8. Discussion on knowledge gaps and future actions for disease burden analysis in key target groups

The publication on pandemic disease burden estimates will be published over the next few months (timeline not specified). The key issues raised during the discussion were that when looking at the mortality multiplier, there was a lack of real quantitative data on co-morbidity factors. It will be helpful to have the mortality rates presented also by age or risk group and not only geographically. Three main groups should be considered are children < 18 years, adults and the elderly. It will be helpful to know if there is an increase in pneumococcal infections during influenza seasons since it was not presented in the analysis.

It was noted that in the USA that the proportion of influenza deaths associated with bacterial infection was not higher during the pandemic than during seasonal outbreaks. The estimation of clinical attack rate is based on the propensity to consult and it differs from one age group to another. There is the limitation of not getting the proportion of asymptomatic infections and this is likely to be similar in all age groups.

The recommendation to be made should be strong and clear on which population groups are to be highlighted and with which vaccine. The risk groups that are known to be at higher risk of

getting severe complications are the elderly, children, pregnant women and people with co-morbidities. These groups applies to both develop and developing countries.

Some regions presented a higher mortality incidence for pandemic (H1N1) 2009 during the period of surveillance, possibly due to the differences in seasonality patterns. Baseline protective immunity might also be different and can have an impact on which populations are more vulnerable.

Some of the questions that the group raised were**:**

1. can we have a mortality ratio for different settings using data from pandemic and seasonal influenza?
2. What can be extrapolated?
3. What are the socioeconomic factors that affect severity and mortality?
4. What are the epidemiological impact of pregnant women, children and the elderly that may not present with fever (the major clinical symptom included in defining influenza-like illness (ILI)?

Extrapolation of disease severity and burden from developed to developing countries may be possible for the following risk conditions:

1. pregnant women
2. people with underlying diseases
3. AIDS/immunocompromised
4. Co-morbidity: incidence/mortality multiplier will be higher in developing countries since control of disease is poorer in such countries.

There is not enough evidence for considering obesity (may be possible for morbid obesity) and being HIV+ as priority risk groups.

Special attention should be considered for vaccination policy for children < 6 moths. Estimation can be performed if data are actively collected. Hospitalization rate in this age group was found to be higher in the USA and might be similar for the rest of the world.

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

The preliminary findings from the 2010 WHO survey for the global mapping of seasonal influenza vaccine were presented. It was noted that data collection is still ongoing and this presentation aimed at only global trends based on limited data. Generalizations and early conclusions from this data cannot be made at this stage.

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.

Findings were described as follow:
Member States with seasonal influenza in national immunization schedule varies from region to region; in AFRO according to the JRF, only Algeria, Mauritius, and South Africa recommend vaccination for specific target groups. In AMRO 91% of the countries have annual seasonal influenza vaccination as part of the national immunization, and one country Dominica is expected to introduce it by 2012. In EMRO, 33% of the countries have an annual seasonal influenza vaccination and one country (Iraq) is expected to do so by 2012. In EURO, information from 27 EU countries showed that all of them recommend seasonal influenza vaccination. In SEARO, only Thailand recently introduced seasonal influenza vaccination. In WPRO, 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 AMRO 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 EURO, 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.

Another aspect that the survey is trying to elucidate is the vaccination coverage by target group. 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 in the majority of the cases the vaccine is free of charge.

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 AMRO, five in WPRO and only one in EURO 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 is 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 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 to be analyzed further. Draft report from the 2010 WHO survey for global mapping use of seasonal influenza vaccine will be available by the end of April 2011.

10. Background and WHO conceptual directions for H5N1 stockpile (notes from EM, commented by CS, JT, NS, JA and M-PK)

- 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 a containment operation in the first country (ies) 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 logistical 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 Pasteur 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 160M 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 H5N (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 8-11 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 and to prepare draft recommendations for consideration by SAGE at its April 2011 meeting.

11. Review the needed information and strategy in relation with stockpile and the use of pandemic vaccines (notes from EM, commented by CS, JT, NS and JA)

- 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 strain 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 doses of pandemic vaccine, the WG considered three main options:
    a) 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.
    b) 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.
    c) 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 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 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 virtual stockpile option with a small physical stockpile of filled doses of H5N1 vaccine for outbreak control would provide maximum flexibility, minimise 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.

12. H1N1 vaccine safety review

The expectations from this session were to discuss the information needed with respect to future policy recommendations for all influenza vaccines in light of the GACVS statement on narcolepsy and Pandemrix, as well as to discuss the tentative plans for a related SAGE discussion at the April 2011 meeting.

<u>The problem statement was formulated as follow:</u>

- 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 GACVS risk assessment 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 WHO position on influenza immunization policy:

On the basis of the risk assessment provided by GACVS, and in consideration of the fact that the regulatory authority of record for the purpose of WHO prequalification, the European Medicines Agency, has not taken any regulatory action, there is no change to the current WHO position on use of pandemic influenza vaccines. 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.

Pandemrix remains on the list of WHO-prequalified vaccines. Long-term implications of the observations on narcolepsy will be considered by SAGE in due course.
The following issues were discussed:

- What information is needed with respect to future policy recommendations for all influenza vaccines in light of the GACVS statement on narcolepsy and Pandemrix
- Plans for a SAGE discussion (if needed) at the April 2011 meeting.

The prevalence outside Finland seems similar to other countries such as Germany, but it is not equally distributed around the world. It will be helpful to review the evaluation and come with generic guidance for adjuvant vaccines.

Pre-licence evaluation and policy for the future, benefit risk for adjuvant and not adjuvant.

The only serious AEFI reported for this vaccine is narcolepsy and it is not the same adjuvant for other vaccines. All adjuvant are different, all influenza vaccine are based on oily adjuvants. There are two new guidelines in Europe on the assessment of pre-clinic and clinical and in combination with antigens.

Narcolepsy is a lifetime condition. It is recommended following up with Finland and monitoring affected individuals. In Finland affected people are asking for compensation.

In AMRO, Pandemrix was used only in those countries that received the WHO donation, there would be a potential liability issue and WHO needs to think about how to tackle this issue if the problem arises. WHO has not received any report of narcolepsy from countries that received

the donated vaccine. The situation in Sweden needs to be clarified, since there is an imbalance between vaccinated and unvaccinated people.

13. Summary of action points and closure

1. Understanding of severity for informing recommendations: revisit again evidences as soon as papers become available and provide evidence for well informed recommendations. Papers on evidence can be shared by emails. An assessment containing all information available will be provided from the secretariat. Joe Breese will help the secretariat in putting it together.
2. Vaccine effectiveness: some consolidated evidence relevant to the topic needs to be scrutinized and will be 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 will likely be similar. This issue will be discussed in the face to face meeting
3. 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 important 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.
4. 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. Information in relation with discussions on the stockpile and the use of pandemic vaccines
    d. Information needed with respect to future policy recommendations for all influenza vaccines in light of the GACVS statement on narcolepsy and Pandemrix.
5. Minutes of the meeting will be available by end of Feb together with the complete set of slides
6. As documents (papers, reports, studies, etc) become available the will be circulated among the Influenza WG members.
7. Sharepoint: A virtual space will be created in order to share all relevant documents, i.e. minutes, slide presentations.
8. 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.
9. Narcolepsy and pandemrix: just as part of the report for this group. Not extra action needs to be taken.

Appendix 1.

WORLD HEALTH ORGANIZATION

2nd MEETING OF THE SAGE WORKING GROUP ON INFLUENZA VACCINES AND IMMUNIZATION

14-15 February 2011
WHO Geneva

AGENDA

Day 1, Monday, 14 February 2011, Room C202

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

Day 2, Tuesday, 15 February 2011, Salle C202

08:30 - 09:00	**Background and WHO conceptual directions for H5N1 stockpile**	***TBD***
09:00 - 11:00	**Review the needed information and strategy in relation with stockpile and the use of pandemic vaccines**	***Led: Chair***
11:00 - 11:30	*Refreshment Break*	
11:30 - 12:15	**H1N1 vaccine safety review**	***David Wood***
12:15 - 12:45	**Discussions on 2011 workplan of the SAGE WG and Summary report to SAGE on 5 April 2011**	***Chair***
12:45 - 13:00	**Summary of action points and closure**	***Chair***

Appendix 2

List of participants

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

WHO Secreatriat
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