Introduction

The Chair summarized the objectives of the Strategic Advisory Group of Experts on immunization (SAGE) Working Group on H5N1 Influenza Vaccine (WG) and the outstanding elements of its agenda today, i.e. to review its recommendations to SAGE on:

- the purpose and dimension of the WHO stockpile of H5N1 vaccine; and
- the use of licensed H5N1 stockpile in persons in potential contact with infected animals.

The outcome of this meeting would be presented to the next SAGE meeting in November 2010.

SAGE recommendation on the WHO H5N1 vaccine stockpiles

A paper was circulated on known and potential H5N1 vaccine stockpiles held in countries and by manufacturers, with their expected shelf-life and replenishment plans. Other countries may be planning to stockpile influenza vaccine for pandemic preparedness purposes. WHO should therefore encourage countries engaging in domestic influenza production, especially large countries, to produce vaccine for their national stockpile with antigen that would be effective to immunize against H5N1 influenza. This may be relevant for countries receiving grants as part of the WHO technology transfer initiative to increase their capacity to produce influenza vaccine, notably China, India and Thailand. It was further recommended that new producers among WHO technology transfer grantees from countries with currently no or very limited seasonal influenza programme should consider stockpiling H5N1 vaccine manufactured during idle periods.

With reference to the stockpiling of adjuvants (both GSK and SP vaccines will be adjuvanted), David Wood agreed that the ECBS would be a good platform to review stability data used for stockpiling adjuvants.

WHO H5N1 vaccine stockpile

Purpose

The original purpose of the WHO H5N1 stockpile was two-fold: (i) rapid containment at the onset of a potential influenza pandemic (estimated need 50 million doses); and (ii) first response by governments for their essential personnel (estimated need 100 million doses). Experience gained from the 2009 H1N1 pandemic, and evidence presented on non-pharmaceutical interventions such as antivirals or personal protective approaches at this meeting, led to agreement that, the use of the stockpile for this purposes might not be practical nor effective. However, strategies for rapid containment were under review internationally and within WHO.

The entire WHO stockpile should thus be targeted to low- and middle-income governments with no immediate access to pandemic influenza vaccine to immunize their essential personnel at the onset of an H5N1 pandemic.
**Vaccine to be stockpiled and its size**
The pledge from GSK and sanofi-pasteur currently amounts to 130 million doses. WHO will try to increase this global commitment, but quantities will not change significantly. The WG was reminded that part of this pledge needed to become a physical stockpile, as required by the WHO Health Assembly. The IVR Secretariat will contact the donor manufacturers to ascertain the quantity of H5N1 they could produce for the physical WHO stockpile during production "windows" within a 12 month period – perhaps around 50 million doses – and negotiate that the remaining doses be available for subsequent "orders" of H5N1 vaccine or as an open pledge to be able to mitigate a pandemic caused by another strain such as H2 or H7.

**Storage of the stockpile**
The physical H5N1 stockpile could be maintained at manufacturers’ sites. Discussion focused on whether the physical stockpile should be stored in bulk or filled and finished product. Fill-finished product would need large financial resources to rotate the stock, as it has a shorter shelf life than bulk product. Moreover, manufacturers may not be willing to stock fill-finished product as it is significantly more bulky. On the other hand, if stored in bulk, fill-finishers, transporters, etc. will need to be identified in advance with pre-agreed contracts and regulatory inspection and approval. Indeed, donor manufacturers expressed concerns about the timing to fill/finish WHO H5N1 vaccine stockpile at the time of a pandemic, and the WHO Secretariat considered that taking physical possession of the vaccine as soon as a pandemic is declared is a priority. In spite of costs, some members recommended that the feasibility of keeping some doses in fill-finished form should be investigated, particularly for health-care workers.

**Size of essential personnel**
Preliminary data on the size of essential workers in countries extracted from H1N1 National Deployment and Vaccination Plans and from the WHO Global Seasonal Influenza Survey indicate a volume representing around 1% of the general population. All countries included health-care workers as a priority group. Excluding countries estimated to be self-sufficient in the event of an influenza pandemic, approximately 1% of 5 billion persons would thus require vaccination, i.e. 100 million doses to immunize 50 million essential personnel. This is well within current commitments. The WHO H5N1 stockpile could be flexible enough to cover extended categories of essential personnel (e.g. up to 2% of global population) subject to the availability of other national stockpiles, and according to country demand.

**Safety data from the H1N1 pandemic**
An updated summary was presented on influenza vaccine safety data, mostly gained from passive surveillance. The safety profile of H1N1 vaccine use has been reassuring. No unexpected safety issues have been identified in the use of adjuvanted versus non-adjuvanted A(H1N1) vaccines. Similarly, severe adverse events such as GBS were no different to other vaccines. The safety profile of H1N1 vaccines will be further reviewed once data on active and long-term surveillance become available.

**Non-pharmaceutical measures**
A paper prepared by the WHO Secretariat was also presented on the effectiveness of non-pharmaceutical methods to interrupt transmission, based on previous influenza pandemics and SARS (the paper did not specifically look at H5). Few published data exist on the various measures such as hand hygiene, quarantining and school closures. Experience with travel restrictions in force during the SARS outbreak led WHO to recommend that only exit, and not entry screening is effective, although members wondered whether this could be successfully implemented in reality. Members also noted differences between personal protective measures and non-pharmaceutical interventions.

* The original pledge of 110 M doses (50M GSK and 60M sanofi-pasteur) were converted to H1N1 (60M GSK and 100M SP), only 30 M of which were used thanks to additional government donations.
SAGE recommendation on the use of licensed human H5N1 influenza vaccine in the interpandemic period in persons in potential contact with infected animals

In April 2009, SAGE recommended that vaccination against H5N1 avian influenza in the interpandemic period "may be recommended" for persons in potential contact with infected animals, depending on a risk–benefit assessment. At that time, knowledge on the safety profile of H5N1 vaccine use was partial and restricted to clinical trial data. Today, given the availability of extensive safety data following the H1N1 pandemic, the WG reviewed the above SAGE recommendation based on a risk–benefit analysis carried out for the WG by US Centers for Disease Control and Prevention and Imperial College, UK. The analysis studied data on H5N1 cases from six countries to evaluate the risk of vaccine-related adverse events against the risk of disease, and thus the likelihood of acceptance of vaccination by four target groups (children, health-care workers, high exposure occupations and all other). It was assumed that the target groups would accept vaccine if the risk from disease exceeded any risk related to vaccination. Depending on the sensitivity analyses against baseline data – duration of protection, vaccine efficacy, number of doses and case–fatality rates – acceptance ranged from zero to the majority. The general public, for example, if unaware of any personal threat, would not volunteer to be immunized, whereas health-care workers in contact with potentially infected patients would be much more willing to be vaccinated.

WG members appreciated the extensive work that had gone into developing the model in such a short space of time. They agreed with the authors on the limitations of the model, e.g. the limited data, inability to weight variables, and heterogeneity within and between groups and countries.

The following refinements were also requested:

- the model should be made more user-friendly for policy-makers, e.g. to be able to assess the level of risk that would make vaccination beneficial;
- the scenario should be the onset of a potential pandemic, thus rates of infection will be much higher than the model has assumed;
- assumptions should be two doses needed for protection and one year duration of protection (it would be important in this respect to collect data on 2009 H1N1 vaccines); sensitivity to vaccine effectiveness lower than 70% (e.g. 50%) should also be considered;
- the model should be adapted for use at sub-national level.

In conclusion, there was consensus in the WG that, although there were more data on the risk of vaccination, more data on the risk of disease were not available, and thus the group found no justification to modify the initial recommendation on the use of H5N1 vaccine in persons in potential contact with infected animals.

With the above adjustments to the model, the WG suggested that it be made available as a useful tool for WHO Member States (and stockpile holders) to input their own data to develop a more accurate risk–benefit analysis. It should be clear, however, that use of the tool and any resulting analysis did not imply the availability of vaccine.

Summary recommendations and next steps

Recommendation on the WHO stockpile

- The entire WHO stockpile should be used to protect essential personnel in case of a pandemic.
- Of the current 130 million dose commitment, a physical H5N1 stockpile should be created based on the quantity that can be produced within the next 12 months, in bulk form. The outstanding doses should remain virtual until a new window of production allows the securing of additional H5N1 doses, or vaccine that can be converted to immunize against whatever strain may be the cause of the next influenza pandemic.
Recommendation on the use of H5N1 vaccine in the interpandemic period for persons in potential contact with infected animals

- There is insufficient evidence on the risk of disease to warrant any change in the original recommendation, i.e. that vaccine "may be recommended" in this target group depending on a risk–benefit analysis.

- To this end, it is recommended that the risk–benefit model developed by CDC, USA and Imperial College, UK be refined and made available by WHO to countries to adapt to their local needs.
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