



## Ad hoc Policy Advisory Working Group on Influenza A (H1N1) vaccines

18 May 2009

The Working Group met by telephone conference on 14 May 2009 to:

1. Review current evidence on influenza A (H1N1) and potential vaccine options,
2. Review the current status of seasonal vaccine production and potential A (H1N1) production capacity, and
3. Discuss timing of a potential recommendation to initiate commercial scale production of A (H1N1) vaccine.

The Working Group was updated on:

- The epidemiology of influenza A (H1N1) infections and associated disease burden;
- The vaccine production capacity for both seasonal and A (H1N1) vaccines based on information provided by vaccine manufacturers;
- Issues related to vaccine efficacy, safety and regulation;
- Programmatic issues.

In its discussions, the group benefited from the input of more than 40 stakeholders through a virtual conference.

Current epidemiological information suggests that the influenza A (H1N1) virus transmissibility potential is at least comparable to that of seasonal influenza viruses, with ability to sustain community spread. There is therefore no reason to expect that ongoing spread of the virus will stop. Although the observed clinical disease severity has so far been mild in most infected persons, there remain critical gaps of knowledge, such as age-related severity, specific risk factors for severe disease, and potential differences in severity in different countries and particularly in developing countries. Currently the influenza A (H1N1) virus is sensitive to oseltamivir and zanamivir and resistant to adamantanes.

A review of 2009 production status for northern hemisphere seasonal vaccine indicates that industry plans to produce approximately 480 million doses of trivalent seasonal vaccine in 2009. Of this, 350 and 430 million doses will be available by 30 June and 31 July 2009, respectively. For influenza A (H1N1), it is estimated that up to 4.9 billion doses could be produced over a 12-month period after the initiation of full-scale production if

1. There is a vaccine yield equivalent to that routinely obtained for seasonal vaccine and
2. There is use of the most dose-sparing formulations.

In this situation, there is a potential access for the UN of supplies of up to 400 million doses.

Currently available data indicate that sera of individuals vaccinated with 07/08 or 08/09 seasonal influenza vaccines do not neutralize the currently circulating influenza A (H1N1) virus. This observation also holds true for sera of individuals vaccinated with adjuvanted seasonal vaccines. This indicates that immunization with recent or shortly to be available trivalent seasonal vaccine is unlikely to provide public health benefits in terms of protection against influenza A (H1N1).

Immunogenicity data for potential pandemic vaccines have already been generated using various vaccine formulations containing H5N1 antigen. However, the optimal antigen content, the required number of doses, the required intervals between doses and the interchangeability of different products is currently unknown for influenza A (H1N1) vaccines. Likewise, the safety profile (including the risk of Guillan Barré syndrome (GBS)) of A (H1N1) vaccines is not yet established, making pre- and post-marketing surveillance imperative. It was noted that it might be difficult to distinguish true vaccine failures from infections with seasonal influenza during a pandemic period.

Before a pandemic vaccine is available, it will be important to establish baseline rates of GBS in different populations so that potential changes in the incidence of GBS associated with influenza A (H1N1) virus circulation and potentially with A (H1N1) vaccines can be detected. This should be a priority in any regions where there is continuing transmission of influenza A (H1N1) in the coming months. In particular, the AFP (Acute flaccid paralysis) surveillance network in the WHO region of the Americas (PAHO) can be used to advantage to collect data.

The Working Group took note that two doses of vaccine may be needed to induce adequate protection, as the global population is immunologically naïve to the new virus. Older adults were shown to possess serum neutralizing antibodies to the new virus, most likely due to cross-immunity with human H1N1 viruses. The combination of A (H1N1) vaccine with trivalent seasonal vaccine would have significant regulatory implications. Therefore, production of a monovalent A (H1N1) vaccine to be used in addition to trivalent seasonal vaccine is the preferred option at this stage.

The Working Group also reviewed the current status of preparation of candidate vaccine viruses and noted that these will likely become available at the end of May 2009. Distribution of these vaccine viruses to vaccine manufacturers may need to be delayed by a further 1 to 2 weeks to allow assessment of their attenuation characteristics in appropriate animal models. Typically one to two additional months are needed by manufacturers after they receive vaccine viruses to isolate rapid growing strains to maximum yield. Based on these considerations, the Working Group concluded that vaccine manufacturers would not be ready to switch to large-scale production before mid-July 2009. In addition, moving into production now could result in starting vaccine production with strains of lower growth potential, as was the case for H5N1 A/Vietnam/2004. With that virus, manufacturers consistently observed yields less than 50% of those usually obtained with seasonal vaccine viruses. Using a poorly growing A (H1N1) virus could reduce global supplies of A (H1N1) vaccine.

After considering the following issues:

1. the need for any recommendation to balance both risks and benefits,
2. the current uncertainty about the severity of influenza A (H1N1) illness,
3. the readiness of vaccine seed strains and reagents for large-scale vaccine production,
4. the current status of production of seasonal vaccine for the Northern hemisphere, and the risks associated with a premature cessation of seasonal vaccine production,

the Working Group considered it premature to recommend that commercial-scale production of influenza A (H1N1) vaccine should start immediately.

The Working Group did make the following recommendations for immediate action:

- (i) The WHO Secretariat, in close coordination with its Collaborating Centers and the Essential Regulatory Laboratories of the WHO Global Influenza Surveillance Network, should recommend which vaccine viruses should be used for vaccine development as soon as possible
- (ii) Essential reagents to calibrate antigenic content should be made available as a priority
- (iii) The WHO Secretariat is encouraged to collaborate actively with its Collaborating Centres, Essential Regulatory Laboratories, and with industry, to assess the growth property of vaccine viruses and identify those with best growth potential, in order to maximize output of vaccine.

- (iv) Manufacturers are urged to develop clinical trial batches and accelerate initiation of clinical trials of influenza A (H1N1) vaccines and to start preparing for a potential future recommendation to move to commercial-scale production.
- (v) The above activities should not interfere with the present production of the Northern hemisphere seasonal vaccines
- (vi) The number of needed doses of A (H1N1) vaccine will depend on the spread of influenza A (H1N1) virus in the next few weeks and on a better definition of the groups to be targeted
- (vii) An evidence-based recommendation for the groups to be targeted for vaccination still requires more data

Finally, the Working Group stressed the fact that clear communications are needed from WHO that declaration of Phase 6 does not automatically mean that WHO is recommending that manufacturers should switch from seasonal to influenza A (H1N1) vaccine production. Likewise, it is important to be clear that a potential recommendation to start production is not considered as a recommendation to start immunizing large population groups.

The Working Group agreed to continue to monitor the evolving situation carefully and made a provisional plan to review the accumulated evidence in the next few weeks to consider whether to recommend initiation of commercial-scale production of influenza A (H1N1) vaccine.

There will also clearly be longer term issues that will need consideration such as the impact of a switch from seasonal manufacturing on subsequent supplies of seasonal vaccine for the Southern hemisphere, the safety and immunogenicity of A (H1N1) vaccine candidates as well as recommendations on the use of A (H1N1) vaccines when they become available.

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Having reviewed the report of the May 14 meeting of the Ad Hoc Advisory Working Group on Influenza A (H1N1) Vaccines, SAGE agrees with its conclusions and recommendations for communication to the Director General of WHO.