Pandemic influenza A (H1N1) 2009 virus vaccine – conclusions and recommendations from the October 2009 meeting of the immunization Strategic Advisory Group of Experts

The Strategic Advisory Group of Experts (SAGE) on immunization reports to the Director-General of WHO on issues ranging from vaccine research and development to immunization delivery. Its remit extends beyond childhood immunization to all vaccine-preventable diseases.1 SAGE met on 27–29 October 2009 in Geneva, Switzerland.2 The following are SAGE’s conclusions and recommendations on pandemic influenza A (H1N1) 2009 virus vaccine. Conclusions and recommendations related to other topics discussed at the meeting will be published in the *Weekly Epidemiological Record* on 11 December 2009.

SAGE was updated on the current epidemiology of pandemic influenza A (H1N1) 2009 virus (hereafter referred to as “pandemic (H1N1) 2009”). As of 17 October 2009, >414 000 confirmed cases and nearly 5000 deaths had been reported to WHO; the actual number of cases is expected to be much higher as public health systems have stopped confirming individual cases and are now monitoring disease trends. When the results of serological studies are published more information will be available on the proportions of populations infected, including mild and non-symptomatic cases. There are fewer data available from developing than developed countries.

As reported to SAGE on 7 July 2009, cases continue to occur mostly in teenagers and young adults, with rates of hospitalization highest in very young children. Between 1–10% of clinical cases have required hospitalization, and 10–25% of hospitalized patients have needed admission into intensive care units (ICUs). A fatal outcome was recorded in 2–9% of hospitalized patients. Pregnant women have a 10 times higher likelihood of requiring admission to an ICU compared with the general population; 7–10% of all hospitalized cases are women in their second or third trimester of pregnancy. Severe outcomes occur more often when underlying medical conditions are present such as chronic lung diseases (including asthma). SAGE found insufficient evidence at this time to classify obesity as an independent risk factor in the absence of co-morbidity. While health-care systems in most countries have been able to cope with the burden of cases of pandemic (H1N1) 2009, a substantial additional burden has occurred, with pressures on emergency wards and ICUs particularly acute in some locations. SAGE considered that its previous recommendations on target populations for prioritizing pandemic vaccination remained appropriate.3

The vast majority of influenza viruses identified worldwide are now pandemic (H1N1) 2009. So far, the virus has been antigenically stable and susceptible to oseltamivir and zanamivir. A limited number of viruses with resistance to oseltamivir have been reported from sporadic cases. SAGE remains aware that evolution of the virus (genetically and antigenically) is unpredictable, especially as the levels of background immunity to this virus build, bringing increased evolutionary pressures on the virus.

Mathematical modelling conducted on southern hemisphere data suggests a 20–40% infection attack rate, with a reproductive rate in the range of 1.1–1.5. The generation time and incubation period appear comparable with those of seasonal influenza. Modelling on vaccination strategies indicates that if vaccination occurs after the peak period of transmission (which may be the case in many northern hemisphere countries), immunization of groups at risk for severe outcomes will be more effective in reducing morbidity and mortality than immunization of groups most associated with transmission of infection.

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1 http://www.who.int/immunization/sage/SAGE_TORs_Full_21_11_08.pdf
2 All presentations delivered at the meeting together with background documents are available at http://www.who.int/immunization/sage/previous/en/index.html
SAGE reviewed data on safety and immunogenicity of pandemic (H1N1) 2009 vaccines. The committee noted that pandemic vaccines (both live attenuated, adjuvanted or non-adjuvanted inactivated vaccine products) produced in Australia, Canada, China, Hungary, the Republic of Korea, the Russian Federation and the USA have been licensed in the above-mentioned countries for use in adults for a single-dose schedule and in some younger and elderly age groups. In Europe, the regulatory authority (EMEA) initially licensed 3 pandemic vaccines (manufactured by GlaxoSmithKline (GSK), Novartis and Baxter) for use as 2 doses. However, after a recent review of new data from clinical studies for the GSK AS03-adjuvanted and for Novartis MF59-adjuvanted vaccines, the EMEA also noted that the data currently available indicate that 1 dose may be sufficient in healthy adults.

SAGE recommended that public health considerations support the use of a single-dose of vaccine in adults and in adolescents aged ≥10 years, provided this use is consistent with the indications of national regulatory authorities. The committee stressed that studies should be undertaken to assess effective dosage regimens in immunodeficient persons for whom 2 doses may be needed. For children aged >6 months and <10 years, little immunogenicity data are currently available. Unless regulatory authorities have advised that a single dose of vaccine is adequate, SAGE recommends that where children have been prioritized for vaccination, then those aged >6 months and <10 years should receive 2 doses of vaccine. In the interests of public health, vaccine supplies should be used to give first doses to as many children as possible, with second doses following as further supplies become available, and subject to regulatory considerations. These recommendations will be updated as more data become available.

Clinical trials investigating the safety and immunogenicity of co-administering seasonal and pandemic vaccines are ongoing. When seasonal and pandemic vaccines are both inactivated, or when one is inactivated and the other is live attenuated, SAGE recommended that they be co-administered. This takes into account public health considerations, as well as the reassuring data to date regarding vaccine safety. In the meantime, the committee recognized the recommendation from the United States Centers for Disease Control and Prevention that live attenuated seasonal and live attenuated pandemic vaccines should not be co-administered.

Based on preliminary results from pharmacovigilance reports, SAGE recognized that there is no indication at this stage that unusual adverse reactions are being observed. So far, the reported adverse events following immunization with either plain inactivated or adjuvanted inactivated vaccines are well within the known safety profile of influenza vaccines. In spite of these preliminary reassuring results, continued vigilance and regular evaluation by health authorities are needed. In view of the public anxieties over vaccine safety that have been reported in the media, SAGE urged that clear messages on the safety of the pandemic (H1N1) 2009 vaccine be communicated to the public and the media.

Reproductive toxicity studies conducted in animal models with non-adjuvanted, adjuvanted inactivated and live attenuated vaccines do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonic or fetal development, and parturition or post-natal development. The licensed indications for use of both adjuvanted and unadjuvanted inactivated vaccines include pregnant women. Moreover, pregnancy is not a contraindication for the use of live attenuated pandemic (H1N1) 2009 vaccine in countries where this vaccine is licensed; attenuation of influenza is based on the incapability of the virus to replicate at body temperature and cause viraemia. In this context, and given the substantially elevated risk for severe outcomes of infection with pandemic (H1N1) 2009 virus in pregnant women, SAGE recommended that, in the absence of a specific contraindication by the regulatory authority or from the WHO prequalification review, any licensed pandemic vaccine can be used to protect pregnant women.
SAGE was updated on the anticipated production capacity for pandemic vaccine over the coming months. This has been revised down from 4.5 billion to 3 billion doses of pandemic (H1N1) 2009 vaccine in the next 12 months. An update was also provided on the WHO initiative to provide pandemic vaccine for developing countries. Around 95 low to middle-income countries, that would not otherwise have access to pandemic vaccines, will be eligible (based on need) to receive support through the initiative. To protect those at greatest risk and to minimize disruption to health-care services, each selected developing country will receive sufficient doses of pandemic vaccine (at 2% of its population) to immunize at least its health-care workers, as recommended by SAGE in July 2009. The WHO secretariat presented to SAGE a summary of ongoing activities aimed at ensuring that developing countries will effectively use the vaccines soon to be provided to them. This includes technical assistance to governments to evaluate adverse events following immunization.

The deployment of sufficient vaccine to cover the first 2% goal in developing countries is expected to occur during November 2009–February 2010. A further goal is to provide each of these 95 countries with enough vaccine to immunize up to 10% of their populations. WHO estimates that, in total, the initiative requires >200 million doses of the pandemic vaccine to be available over the next 6–12 months. SAGE emphasized the importance, for all countries that have not yet done so, of developing a comprehensive national strategy for the use of pandemic vaccine.

SAGE reviewed the options for southern hemisphere seasonal influenza vaccine formulations for use in 2010. These include a trivalent vaccine (strains of A (H1N1) 2009; A (H3N2); and B) or, alternatively, a bivalent vaccine (strains of A (H3N2) and B) and a separate monovalent pandemic (H1N1) 2009 vaccine. SAGE recognized the increased programmatic complexities associated with the use of 2 separate products (bivalent and monovalent influenza vaccines) rather than of a trivalent product. However, SAGE also recognized that the bivalent + monovalent option was being requested by certain southern hemisphere countries, and that this option had the advantage of increasing availability of pandemic (H1N1) 2009 vaccine since it would allow increased quantities of adjuvanted influenza A (H1N1) 2009 vaccine to be produced compared with production of unadjuvanted vaccine, thereby maximizing the availability of pandemic vaccine. SAGE concluded that both the trivalent and the bivalent + monovalent options should be available for formulation for 2010 southern hemisphere seasonal influenza vaccine production, subject to national needs. SAGE encouraged southern hemisphere countries that choose to use trivalent vaccine to donate any surplus monovalent A (H1N1) 2009 vaccine supplies to the WHO initiative.