



Prospects for International Harmonization of the Regulatory Processes for MCM

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**World Health
Organization**

Outline

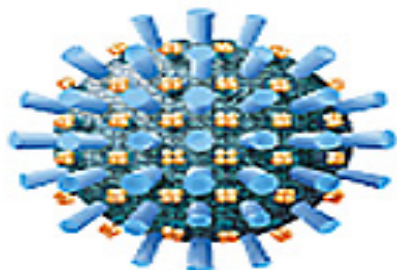
- Pandemic H1N1 vaccine as a case study
 - context
 - regulatory and safety considerations to support worldwide vaccine deployment
- Conclusions



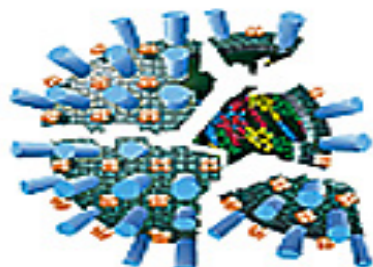
Context



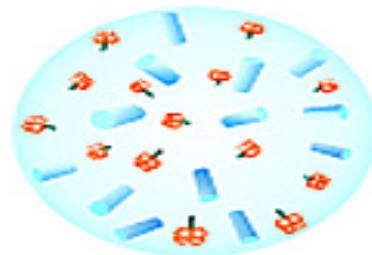
Types of licensed monovalent pandemic influenza A (H1N1) 2009 vaccines



Whole virus

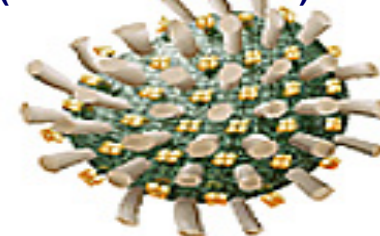


Split virus



Subunit
(surface antigen)

(Source: IFPMA-IVS)



Live attenuated

<p>Baxter (EMEA)</p> <p>Omnivest (Hungary)</p>	<p>8 manufacturers, (China)</p> <p>CSL (Australia; US)</p> <p>Sanofi Pasteur (US)</p> <p>Green Cross (Korea)</p> <p>GSK ASO3 (EMEA, Canada)</p>	<p>Novartis (US)</p> <p>Novartis+M59 adjuvant (EMEA)</p>	<p>MedImmune (US)</p> <p>Microgen (Russia)</p>
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Current status of pandemic (H1N1) 2009 vaccine donation to WHO

- Donations from manufacturers: GSK, Sanofi Pasteur, CSL, MedImmune
156 million doses
- Donation from 12 governments of up to 10% of domestic vaccine supply (or equivalent capacity, or cash, or mixture of the above): Australia, Brazil, France, Germany, Italy, Japan, New Zealand, Norway, Switzerland, Thailand, UK and USA
Up to 50 million doses?
- Delivery schedule: starting end November 2009 over a 12 month period
- Prequalification of H1N1 vaccines: expected October 2009 to early 2010 for vaccine donated to WHO

Basket of principles for defining the sequence of distribution of WHO H1N1 pandemic influenza vaccine (following SAGE advice, not in ranking order)

● Vulnerability considerations

- Geography: in the first 6 months (starting November): 2/3 of supplies to the Northern hemisphere, 1/3 to SH, because number of cases in the decline currently in the SH, and rising in the North; after April 2010, 2/3 SH, 1/3 NH.
- Disease burden: in the same hemisphere, countries with highest ratio of death/inhabitant will be served first.

● Readiness considerations

- Programmatic aspects: i.e. readiness to vaccinate (plan, logistics, priority groups identified etc).
- Contractual arrangements: fulfillment of legal requirements (waiver registration, assume liability, etc as per country letter of agreement)



Regulatory considerations



Regulatory preparedness

- regulatory authorities have been generally well prepared and have responded vigorously to the need to facilitate rapid development of H1N1 vaccines, whilst retaining a proportionate degree of independent oversight of quality, safety and efficacy of candidate products
- through WHO there has been over several years, and continues to be, international information exchange and consensus-building between authorities
- communicating the scientific basis for regulatory decision-making is key to this effort



Regulatory data requirements

- In general, regulatory data requirements have varied with the level of pre-existing knowledge of the candidate vaccine
- Candidate vaccines produced with already licensed processes, were licensed on the basis of laboratory tests only; clinical data have been required as a post-licensure commitment
- Candidate vaccines produced using novel technologies have required a full regulatory package and correspondingly lengthier time to licensure
- WHO prequalification is available for H1N1 vaccines to address the needs of countries receiving vaccine via UN supply



Quality related issues

- International consensus was in place prior to the pandemic on key quality specifications for pandemic influenza vaccines. Nevertheless, some issues have occurred:
 - Reagents to calibrate the majority of candidate vaccines using conventional potency tests were qualified (just) in time prior to initiation of clinical trials
 - In some cases candidate vaccines were available ahead of the reagents; authorities were flexible and validated alternative potency tests were accepted to enable clinical trials to proceed
- H1N1 vaccines are (mostly) in multi-dose vials; preservatives have been required by regulators; this is different to the usual single-dose presentation and has caused communications problems in some countries
- Regulators have required expiry dates on vial labels



Efficacy related issues

- All authorities have required clinical trials be done by manufacturers to confirm that the selected dose and schedule is immunogenic; criteria for assessment of immunogenicity as per 2007 WHO guidance
- Real-time negotiations, facilitated by WHO, have been necessary to address unforeseen issues
 - e.g a better yielding vaccine strain was identified after clinical trials were initiated; authorities agreed that additional clinical trials need not be done, unless the HA or NA antigens were manipulated to obtain improved yields
- Not all questions are being answered by the manufacturer's clinical trials and additional studies by public health authorities are being conducted to answer questions such as effect of concomitant administration of monovalent H1N1 flu and trivalent seasonal flu vaccines
- Additional processes have been needed to translate regulatory decisions into public health practice – eg that 1 dose is sufficient from age 6mos.



Safety related issues

- There is relatively little experience with population-wide use of adjuvanted influenza vaccines; special attention is therefore needed to monitor the safety of such vaccines as they are deployed on a large-scale
- International collaboration on influenza-vaccine specific safety surveillance and risk communication post-large scale use of A (H1N1) vaccines will be essential and is being developed at present



Context of vaccine safety discussions

- Safety concerns expressed outside of scientific context and by media are repeatedly raised
- Vigorous anti-vaccine campaigns are occurring in several parts of the world
- Effective communication responses for both lay and scientific audiences are needed

Public concerns about the safety of pandemic H1N1 influenza vaccines

● Guillain–Barré syndrome

(GACVS 2009)

- the underlying reasons for the association observed in 1976 are unknown

- since then, either no association with GBS or, in a few studies, a very small risk (app. 1 case/1.000.000 vaccinations)

- importance of preparing for active surveillance for GBS syndrome and availability of background rates

● Adjuvanted influenza vaccines

(GACVS 2009)

- relatively small scale experience, especially in risk groups

- potential for higher reactogenicity

- autoimmune events following immunization

● Squalene (GACVS 2006)

- fears of squalene in vaccine inducing pathological anti-squalene antibodies are unfounded

- but experience of squalene-containing vaccines has been primarily in older age-groups

<http://www.who.int/wer/2006/wer8128.pdf>

● Thiomersal (GACVS 2008)

- no evidence of toxicity in infants, children or adults exposed to thiomersal in vaccines

● Risks in special groups (eg. pregnancy)

- Risk-benefit of influenza vaccination during pregnancy, at all stages,

- given the high risk to the mother - and thus to the fetus - of the disease itself, and (as far as is known) the small potential risk to mother and fetus of the seasonal inactivated influenza vaccine, SAGE made recommendations in July 2009.

- current SAGE recommendation has been clarified



Conclusions



Regulatory harmonization

- Preparations over several years have resulted in a relatively high degree of regulatory preparedness and harmonization for pandemic influenza vaccines
- As with all preparedness plans, real-time adjustments have been necessary, which requires strong international networking arrangements
- Not all questions relevant to public health practice have been addressed by manufacturers – public health R&D is needed
- Translation of regulatory decisions into public health policy requires another set of harmonized actors and activities





Evaluation of immunogenicity: Pandemic influenza A (H1N1) 2009 vaccines (inactivated)

- Serological criteria to assess immunogenicity (WHO – ECBS 2007, EMEA) follow criteria established for seasonal influenza vaccines:
 - proportion of seroconversions should be >40%
 - increase in geometric mean titre (GMT) should be >2.5-fold
 - the proportion of subjects achieving an HI titre ≥ 40 (or single radial haemolysis (SRH) titre $>25 \text{ mm}^2$) should be >70%
- All three criteria should be met and it is desirable they are exceeded
- Note of caution (1): Correlation between HI titre and protection may not be as strong for vaccines against novel human influenza viruses for which the human population is immunologically naïve as for seasonal influenza vaccines.
- Note of caution (2): Serology results can vary between laboratories - availability of an international standard for pandemic H1N1 antibody will facilitate comparisons

Evaluation of Immunogenicity: pandemic influenza A (H1N1) 2009 vaccines (live attenuated)*

- Determination of neutralizing, haemagglutination inhibition, or single radial haemolysis antibodies in blood
- Since LAIV are most likely to be administered by the respiratory route, immune parameters other than antibodies in blood should also be assessed.
- Clinical endpoint studies provide the definitive assessment of efficacy of LAIV.

*WHO ECBS 2009