Update on immunogenicity of pandemic influenza A (H1N1) vaccines:

Preliminary results from clinical trials

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QSS/IVB/WHO
SAGE, 28 October 09, Geneva
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 mm²) 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
Immunogenicity results (Australia)

Conclusions from preliminary results

- One 15 mcg dose CSL monovalent A (H1N1) 2009 vaccine = highly immunogenic in healthy adults

- HI titre ≥ 1:40 at baseline in 1/3 participants possibly due to cross-reactive antibodies to seasonal strains and/or subclinical & mild H1N1v infections in the community
Cross-reactive antibody responses to 2009 pandemic A (H1N1) virus
Hancock et al., New England Journal of Medicine, 10 September 2009

- Assessed pre-existing immunity and evaluated seasonal vaccine strategies by measuring cross-reactive antibody responses (micro-neutralization assay)

- Tested human sera from blood donors or recent seasonal- or 1976 swine influenza vaccinees

- Results: cross-reactive antibodies against 2009 A (H1N1) virus
  - 4/107 persons (4%) born after 1980 had pre-existing cross-reactive antibody titres of >40
  - 39/115 persons (34%) born before 1950 had titres of >80
  - Inactivated trivalent seasonal influenza vaccination increased cross-reactive antibody by factor of >4 in 0/55 aged 6 mo-9 yrs, 12/231 aged 18-64 yrs, and 5/113 aged 60 yrs
  - Adjuvanted seasonal vaccination did not further enhance cross-reactive antibody
  - A/New Jersey/1976 swine influenza vaccination substantially boosted cross-reactive antibodies
Conclusion

- Recent seasonal non-adjuvanted or adjuvanted influenza vaccination induced little or no cross-reactive antibodies to pandemic influenza A (H1N1) 2009 virus in any age group
- Persons aged \(<30\) had little evidence of cross-reactive antibodies
- A proportion of older adults had pre-existing cross-reactive antibodies
**Types of licensed monovalent pandemic influenza A (H1N1) 2009 vaccines**

(Source: IFPMA-IVS)

<table>
<thead>
<tr>
<th>Whole virus</th>
<th>Split virus</th>
<th>Subunit (surface antigen)</th>
<th>Live attenuated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter (EMEA)</td>
<td>CSL (Australia; US)</td>
<td>Novartis (US)</td>
<td>MedImmune (US)</td>
</tr>
<tr>
<td>Ommnivest (Hungary)</td>
<td>Sanofi Pasteur (US)</td>
<td>Novartis+M59 adjuvant (EMEA)</td>
<td>Microgen (Russia)</td>
</tr>
<tr>
<td>8 manufacturers, (China)</td>
<td>Green Cross (Korea)</td>
<td>GSK ASO3 (EMEA, Canada)</td>
<td></td>
</tr>
</tbody>
</table>
### Monovalent pandemic influenza A (H1N1) vaccines*: immunogenicity in healthy adults (18+)

<table>
<thead>
<tr>
<th>Manufacturer (Licensing agency)</th>
<th>No. doses</th>
<th>Number of serological criteria exceeded</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL (Australia; US-FDA)</td>
<td>1</td>
<td>3/3</td>
</tr>
<tr>
<td>GSK/ASO3 adjuvanted (Health Canada)</td>
<td>1</td>
<td>Data not yet available</td>
</tr>
<tr>
<td>Sanofi Pasteur (US-FDA)</td>
<td>1</td>
<td>3/3</td>
</tr>
<tr>
<td>Novartis/Mf59 adjuvanted (EMEA)</td>
<td>1**</td>
<td>3/3</td>
</tr>
<tr>
<td>Green Cross (Korea FDA)</td>
<td>1</td>
<td>3/3</td>
</tr>
<tr>
<td>MedImmune (US-FDA)</td>
<td>1</td>
<td>Not applicable to live vaccines</td>
</tr>
</tbody>
</table>

*Vaccines offered to WHO  
** EMEA consider 1 dose could be acceptable but prefer 2 doses be used
Monovalent pandemic influenza A (H1N1) vaccines - immunogenicity in healthy adults (18+)

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<th>Manufacturer (Licensing agency)</th>
<th>No. doses</th>
<th>No. serological criteria exceeded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinovac and 7 other vaccines from China (SFDA)</td>
<td>1</td>
<td>3/3</td>
</tr>
<tr>
<td>GSK/AS03 adjuvanted (EMEA)</td>
<td>1**</td>
<td>3/3</td>
</tr>
<tr>
<td>Baxter (EMEA)</td>
<td>1***</td>
<td>3/3</td>
</tr>
</tbody>
</table>

# Vaccines not currently donated to WHO

** EMEA consider 1 dose could be acceptable but prefer 2 doses be used

*** EMEA prefer 2 doses to be used; additional data expected for review
Preliminary paediatric and elderly data

- Australia pediatric data: 21 days post first dose
  - CSL product meets 3/3 serological criteria for 3-9 yr age group; data on younger age group pending

- USA pediatric data: 21 days post first dose
  - Sanofi Pasteur product meets sero-conversion criteria in the 9 yr old group but not the 3 yr old group
  - CSL product – data expected mid November

- Results from on-going paediatric clinical trials in Europe, China, South Korea expected early November

- Note: for seasonal influenza vaccines, WHO recommends 2 doses for children

- Results from on-going clinical trials in elderly expected in early November
Co-administration

- Clinical trials of co-administrating seasonal trivalent and monovalent pandemic influenza A (H1N1) vaccines are ongoing; regulatory opinion expected November or December
Conclusions

- Both adjuvanted and non-adjuvanted Influenza A (H1N1) 2009 vaccines induce high level immune responses in healthy adults in clinical trials.

- Non-adjuvanted and live attenuated vaccines have been licensed in China, Australia, USA, Hungary, Russia, Rep of Korea for use in adults using a single dose schedule.

- Adjuvanted vaccines have been licensed by EMEA with a two-dose recommended schedule, but with the comment:

  - However, preliminary immunogenicity data obtained at three weeks after administration to a limited number of healthy adults aged 18-60 years suggest that a single dose may be sufficient in this age group.

- In view of the scarcity of influenza A (H1N1) 2009 vaccine in the coming months, SAGE may consider recommending that public health considerations warrant the use of a single dose of vaccine in adults.
Immunogenicity results (Sinovac, China)
Reverse cumulative distribution curve (HI titres against X-179A)
21 days post first dose

Unpublished data from Sinovac

Unpublished data from Sinovac