Minutes: Consultation on Immunological Endpoints for LAIV Clinical Trials, 2 December 2009

EXECUTIVE SUMMARY

Background
WHO has recently been able to provide three developing country vaccine manufacturers with a license on the Russian Live Attenuated Influenza Vaccines (LAIV) technology: Serum Institute of India (SII), Government Pharmaceutical Organization of Thailand (GPO Thailand), and Zhejiang Tianyuan Bio-pharmaceutical Company in China. Two vaccine manufacturers, GPO Thailand and SII, are finalizing protocols for clinical trials of influenza A(H1N1) 2009 LAIVs. Both manufacturers have provisionally planned, by default, to use the same immunological criteria used for the evaluation of inactivated influenza vaccines. To advise manufacturers on the design of clinical trials for LAIVs, the WHO organized a virtual consultation on 2 December 2009. The consultation included 7 participants from manufacturers and trial clinicians, 6 experts in the field of influenza vaccine clinical trials, 3 observers from the US CDC, and 2 participants from WHO Initiative for Vaccine Research.

Immunological endpoints
Participants discussed the appropriate laboratory testing that should be used to assess immune response in LAIV clinical trials. There was consensus that as the "gold standard" hemagglutination inhibition (HAI) assays should be used as the primary method for immune response detection. Microneutralization (MN) can also be done, but should not be seen as part of the critical path, but as an additional or secondary endpoint. Although the U.S. Food and Drug Administration has not used IgA serology for vaccine evaluation, IgA ELISA assays may be considered as an exploratory secondary endpoint where the assay is considered to be robust. There was consensus that it is not possible to establish specific thresholds for immunological endpoints as has been done for the inactivated vaccines. Therefore, the experts agreed that an appropriate approach to evaluating the immunogenicity of LAIVs in clinical trials would be to show "significant uptake" (e.g., a majority of vaccinees respond) in children 12-59 months as measured by combining results from a panel of tests that could include HAI, MN, serum IgG, nasal IgA, and evidence of vaccine virus shedding and replication. In adults, immunological endpoints are expected to be less relevant for LAIV immune response evaluation (but clinical trials are still necessary for safety evaluation); however, it may be possible to detect immune responses in adults, as most people will be susceptible to the novel H1N1, and evidence of immune response in adults was recorded in recent H1N1 LAIV clinical trials in Russia.
Clinical trial design--comparator group

There was clear consensus that there must be placebo control (saline, or formulation buffer) in the clinical trials, and that if possible it would be beneficial to include an active control arm to establish safety and immunogenicity relative to licensed vaccines. Preference for selection of active control was ranked in the order: pandemic H1N1 MedImmune LAIV >> pandemic H1N1 Russian LAIV >> seasonal MedImmune LAIV (FluMist™); however, it was recognized that active control vaccine availability and regulatory issues within clinical trial site countries (particularly in India) would influence the use/non-use of these active controls. The use of an inactivated vaccine as an active control was deemed inappropriate. With or without the inclusion of an active control, it was also recommended that comparative serology be done in an independent laboratory, if possible comparing serology from specimens collected during the GPO Thailand and SII clinical trials with the specimens collected during the MedImmune and Russian LAIV trials.

Recommendations

Age groups
1. The protocols should include evaluation of immunogenicity and safety in all age groups ≥ 1 year of age.
2. Immunological evaluation should focus on children 12 - 59 months of age, as this age group is expected to have the most robust immune response that can be readily assessed in these clinical trials.
3. Although not the focus for vaccine evaluation, immunological evaluation should also be done for adults.

Immunological Assays
4. Hemagglutination inhibition (HAI) should be used as the primary method for immune response detection.
5. LAIV evaluation criteria should not include specific immunological thresholds, as these are not well-defined for LAIVs.
6. In place of specific threshold criteria, "significant uptake" (e.g., a majority of vaccinees respond) as measured by combining results from a panel of tests that could include HAI, MN, serum IgG, nasal IgA, and evidence of vaccine virus shedding and replication.

Trial design/Comparator group
7. The inclusion of an active comparator arm would be beneficial, with preference in the order: pandemic H1N1 MedImmune LAIV >> pandemic H1N1 Russian LAIV >> seasonal MedImmune LAIV (FluMist™).
8. Comparative serology should be done in an independent laboratory, if possible comparing serology from specimens collected during the GPO Thailand and SII clinical trials with the specimens collected during the MedImmune and Russian LAIV trials.

9. To fully assess 1 vs. 2 doses of vaccine, the following clinical trial design is suggested:

   Group 1: vaccine Day 0, placebo Day 21, immune assessment Day 0, Day 21 and Day 42
   Group 2: vaccine Day 0, vaccine Day 21, immune assessment Day 0, Day 21 and Day 42

Background

The WHO organized a virtual consultation on 2 December 2009 with the clinicians of GPO Thailand and Serum Institute of India and 6 experts in the field, with the following objectives:

- Reviewing appropriate immunological endpoints to evaluate the immunogenicity of pandemic LAIV;
- Proposing possible pandemic LAIV clinical trial design (comparator groups?); and,
- Identifying criteria for licensing which could be proposed to National Regulatory Authority without experience in reviewing LAIV registration dossiers.

Agenda (noted times are for Geneva-GMT+1)

Moderator: Dr. Marie-Paule Kieny, Director, WHO Initiative for Vaccine Research

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Description</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>3:45 pm - 4 pm</td>
<td>Establish connection with participants</td>
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<tr>
<td>4 pm - 4:15 pm</td>
<td>Welcoming of participants, background and objectives of the consultation</td>
<td>MP Kieny</td>
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<tr>
<td>4:15 pm - 5:15 pm</td>
<td>Discussion: What are appropriate immunological endpoints for evaluating pandemic LAIVs in clinical trials?</td>
<td>Plenary</td>
</tr>
<tr>
<td>5:15 pm - 5:45 pm</td>
<td>Discussion: Is there need for a comparator group in pandemic LAIV clinical trials? If so, what is the most appropriate control vaccine?</td>
<td>Plenary</td>
</tr>
<tr>
<td>5:45 pm - 6 pm</td>
<td>Summary and next steps</td>
<td>MP Kieny</td>
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See Appendix 1 for the List of Participants and Appendix 2 for the Consultation Minutes.
## Expert Consultation Participants

<table>
<thead>
<tr>
<th>Experts</th>
<th>Affiliation</th>
<th>Contributions</th>
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<tbody>
<tr>
<td>Dr. Robert Belshe</td>
<td>St. Louis University School of Medicine Center for Vaccine Development</td>
<td>Has led several of the NIH sponsored clinical trials developing LAIV monovalent vaccine strains in the US for the past 30 years. These studies evaluated the safety, immunogenicity and efficacy of LAIV strains in adults and children. More recently he led the pivotal placebo-controlled efficacy field trial of trivalent LAIV in children; he also led the subsequent head to head trial of LAIV vs TIV to compare the safety and efficacy of the two vaccine approaches in young children.</td>
</tr>
<tr>
<td>Dr. Frank Malinoski</td>
<td>TD Consultancy, LLC</td>
<td>Twenty five years of preclinical, clinical, regulatory, medical affairs (post-licensure), safety, business development (including board membership), and policy experience across a wide array of vaccines. At Wyeth (2000 to 2004), supported both inactivated vaccine and partnership with Aviron then MedImmune in both Medical Affairs and Business Development. At MedImmune ran Medical Affairs support for FluMist from Dec 2005 to Apr 2009.</td>
</tr>
<tr>
<td>Dr. Paul Mendelman</td>
<td>Chief Medical Officer LigoCyte Pharmaceuticals Bozeman, Montana</td>
<td>Has over 20 years of experience in academic, clinical and pharmaceutical research with a specialization in pediatric infectious diseases. Managed the clinical development group for FluMist™, the first and only intranasal influenza vaccine available in the U.S.</td>
</tr>
<tr>
<td>Dr. Arnold Monto</td>
<td>UM School of Public Health</td>
<td>Professor of Epidemiology</td>
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</table>
### Appendix 1: CONSULTATION PARTICIPANTS

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<td>Has served as PI or Co-investigator for several clinical trials of LAIV vaccines, in normal and immunocompromised hosts, primarily in children. These have included studies of its safety and viral shedding, immunogenicity, efficacy, effectiveness, and cost-effectiveness, funded by industry, CDC, and/or NIH. Has also conducted studies of population-based influenza epidemiology and prevention and control of nosocomial disease. Has led or participated in several phase II and IV studies of inactivated seasonal and avian influenza vaccines in adults and children.</td>
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<td>Senior Advisor on disease control and Chairman of the oversight committee for influenza vaccine production of the GPO Thailand.</td>
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</table>
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<table>
<thead>
<tr>
<th>Name</th>
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<th>Email Address</th>
<th>Contact Information</th>
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<tbody>
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Dr. Punnee Pitisuttithum is a Professor and Head of Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University. Working in the field of vaccines against infectious diseases, clinical research and development area, e.g., HIV vaccine, HPV vaccine, cholera vaccine, shigella vaccine, etc., and now flu vaccine.

Mr. Sit Thirapakpoomanunt is the Director of the Viral Division, GPO Thailand.

Dr. Prasad Kulkarni is a Clinical Pharmacologist working in the field of vaccine clinical research for the last 10 years. He has worked on Measles, Rubella, MMR, DT, DTP, DT, Hepatitis B, Rabies, BCG, Meningitis, Hib, Combination (e.g., DTP-HBV, DTP-HBV-Hib), aerosol measles vaccines. He has also worked on immunoglobulins and monoclonal antibodies. Apart from clinical trials, he is also involved in pharmacovigilance, regulatory activities, and support marketing activities.

Dr. Rajeev Dhere is an employee of Serum Institute of India (SII).

Dr. Leena Yeolekar is an employee of Serum Institute of India (SII).

Dr. Chen Xuekui is the Deputy General Manager of Zhejiang Tianyuan Bio-pharmaceutical Co., Ltd.
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Appendix 2: CONSULTATION MINUTES

A) Welcome and background by Dr. Marie-Paule Kieny / WHO

Dr. Kieny welcomed the participants and presented the background and objectives of the consultation. GPO and SII ready to move into clinical trials of the Russian vaccine. To seek advice for the manufacturers from the experts on the design of the clinical trials of the LAIVs and to summarize for national regulatory authorities who have to review the results of the clinical trials prior to authorizing use of this vaccine.

- To come to a consensus on the appropriate immunological endpoints for the evaluation of LAIV in the upcoming clinical trials.
- To seek advice on an appropriate control group for the upcoming LAIV clinical trials.

Not to provide advice to regulators, as this is being done through another stream of work.

B) Discussion: What are appropriate immunological endpoints for evaluating pandemic LAIVs in clinical trials?

Mendelman
- HAI is the "gold standard".
- MN is more sensitive, so also recommended.
- Serum IgA/IgG by ELISA not standard, but easy to do, so can be done.
- Mucosal IgA was not successful at MedImmune and results from other sites have not been reproducible, as the technology is not in place to get robust nasal IgA data.
- Data shows that it is better to focus on young children (12-59 months) in order to measure immune response to LAIV.

Belshe
- Focus on young children for immunogenicity and safety.
- Vigorous HAI in children so may not be necessary to do MN.
- Difficult to do nasal wash IgA in field trials and it is an investigation assay.
- In adults, not likely to find antibody response as measured by HAI and MN. Probably secretory IgA and cellular immune response, which are difficult to measure.

Rudenko
- Experience has been to combine results from several tests, including HAI, IgA from nasal swabs, IgG from serum, and MN (see Appendix 3).
- IgA nasal swabs are difficult, but if people have experience, it is worthwhile. Reference Peter White (NIH) for methodology in children.
- Recommend 2 doses for clinical trials, but to assess immune response after 1 dose also.

Malinoski
- HAI is "gold standard".
- Strains used for HAI are important.
- Nasal IgA is difficult and may not be useful in terms of licensure, i.e., FDA is not using IgA data.
- Focus on younger children, but data in seronegative adults will be important.

Pitisuttithum
- Will also use EliSpot for IgA with support from IVI (Korea).
Appendix 2: CONSULTATION MINUTES

Belshe
- Proportion of young children (e.g. 80-90%) with any evidence of infection with vaccine virus. No established serum antibody level that correlates with protection for a nasal vaccine. No immunological thresholds. This would not be relevant in adults.

Malinoski
- Would not set any thresholds.
- Combining any and all assays is a reasonable approach. MedImmune also has used this approach.
- Most adults should be seronegative to the novel H1N1, so it will be interesting to look at results in adults as well.

Zangwill
- General assessment of response appropriate with no specific immunological thresholds.
- Important to have young children for immunogenicity and safety.

Rudenko
- Licensing in Russia was based upon safety data, not immunological thresholds.

Monto
- Would support the use of viral shedding to indicate vaccine take.
- Also supports including young children.

Mendelman
- In support of using shedding as an endpoint, a Finnish study of children in day care showed shedding in approximately 80% of vaccinees in 12 days after vaccination.
- Safety has to be tested in all ages.

Belshe
- Use homologous antigen for HAI assays, and should not matter if the origin is TIV or LAIV.

C) Discussion: Is there need for a comparator group in pandemic LAIV clinical trials? If so, what is the most appropriate control vaccine?

Belshe
- The most appropriate comparator would be the available live vaccine in a double-blind trial of safety and immunogenicity in all age groups of the 2 live vaccines.

Malinoski
- The use of different applicators are used for the different arms, there will be issues with double-blinding.

Monto
- Support the use of an active comparator. There would not be a lot to gain from using an inactivated vaccine for comparator.
- A large placebo group is necessary to tease out concurrent infections for safety assessment.
Appendix 2: CONSULTATION MINUTES

Kulkarni
- No LAIVs are licensed in India, which constrains using an active comparator in India, especially when considering the timeline for the clinical trials.

Pitisuttithum
- Using only placebo may raise ethical issues, so may be better to use seasonal flu vaccine?

Mendelman
- Recommend comparators for immunogenicity and safety.
- Also should keep the saline control for safety evaluation.
- It may useful as an internal validation to use the inactivated vaccine that is in use in the countries.

Belshe
- Not ideal, but the trivalent seasonal live vaccine would give important information if the monovalent cannot be accessed.
- All age groups should be included with the comparator.

Malinosky
- Comparative serology with serum from MedImmune trials, using a single independent laboratory for specimens from both Thailand and India.
- Preferable to have the appropriate comparator than worry about the double-blinding.

Rudenko
- Using inactivated vaccine comparator is not appropriate.
- Devices and colors of vaccines are different, so blinding would be difficult.

Dhere
- Active comparators would be difficult for India, given the regulatory issues already mentioned.
- The placebo presentation is exactly the same as the active component.
- Already connected with a laboratory for HAI and MN analysis. Can make aliquots for comparative serology studies.

Malinoski
- Would not consider the use of inactivated vaccine as comparator.

D) Meeting summary and recommendations by Dr. Marie-Paule Kieny / WHO

See the Executive Summary.
### Antibody Responses in volunteers vaccinated with Live Attenuated Reassortant Influenza Vaccine

*A/17/California/2009/38(H1N1)*

(Volunteers with HAI serum Ab titers ≤ 1:10 before vaccination)

<table>
<thead>
<tr>
<th>Interval between 1st and 2nd vaccinations</th>
<th>Number of persons</th>
<th>Sample</th>
<th>HAI test (blood serum)</th>
<th>% of persons with reliable Ab conversions</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>GMT</td>
<td>Ab titers ≥1:20</td>
</tr>
<tr>
<td>10 days*</td>
<td>46</td>
<td>I</td>
<td>5.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>6.5</td>
<td>3 (6.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>15.4</td>
<td>25 (54.3%)</td>
</tr>
<tr>
<td>21 days**</td>
<td>47</td>
<td>I</td>
<td>5.4</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>II</td>
<td>8.8</td>
<td>12 (25.5%)</td>
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<tr>
<td></td>
<td></td>
<td>III</td>
<td>11.0</td>
<td>16 (34.1%)</td>
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<td>Placebo</td>
<td>19</td>
<td>I</td>
<td>6.5</td>
<td>1 (11.1%)</td>
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<tr>
<td></td>
<td></td>
<td>II</td>
<td>8.4</td>
<td>2 (22.2%)</td>
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<tr>
<td></td>
<td></td>
<td>III</td>
<td>9.0</td>
<td>2 (22.2%)</td>
</tr>
</tbody>
</table>

* I – before first vaccination; II – 10 days after first vaccination; III – 21 days after second vaccination.

** I – before first vaccination; II – 21 days after first vaccination; III – 21 days after second vaccination.

*** Number (%) of volunteers with Ab conversions detected in one or more tests.