

# **Summary of: WHO Virtual Scientific Consultation on the use of Live-attenuated Influenza Vaccines (LAIV) Against the H1N1 Pandemic Virus**

*Held by teleconference on August 7, 2009 15:00-17:00 CET*

A consultation was held by teleconference to review LAIV efficacy and potential safety issues that will facilitate planning and clinical trial design for H1N1 vaccines.

The purpose of this consultation was two-fold:

- (1) To review the immunogenicity and effectiveness of LAIV, as well as potential safety concerns associated with using LAIV, in the current H1N1 pandemic.
- (2) To discuss experience with, and options for, alternate delivery devices for LAIV.

Participants in the teleconference included vaccine manufacturers, scientific experts on influenza vaccines and safety evaluation, as well as representatives from regulatory agencies, WHO and other stake-holders.

## **Introduction**

In light of the recent widespread outbreak of the novel influenza A (H1N1) virus, there is a need in the immediate future to immunize large population groups. Global supply of pandemic vaccine is limited. Live attenuated influenza vaccines (LAIV) can expand the supply of influenza vaccines given that yields of vaccine are significantly higher with LAIV, compared to inactivated influenza vaccines (IIV), yielding between 60 to 100 doses of vaccine per egg. The delivery of the LAIV has traditionally used a spray device. There is a potential to make more doses than there are spray devices available. Alternative delivery means are required to facilitate mass vaccination with LAIV.

LAIV have been licensed in the Russian Federation for over thirty years and in the United States since 2003 for the prevention of seasonal influenza where they have been shown have an approximately similar level of efficacy compared to IIV. Safety of LAIV has been evaluated in tens of thousands of adults and children from 2 years of age and above and more than 100 million doses have been distributed. LAIV have also been evaluated in clinical studies for potential to be used in the event of an avian influenza pandemic. While licensed for seasonal vaccine use, these have not yet been used for pandemic control.

In order to make informed decisions regarding the use of LAIV in pandemic control, the WHO held this non-confidential consultation to discuss vaccine efficacy, delivery and potential safety issues that will facilitate planning and clinical trial design. The outcomes from this meeting will inform subsequent confidential dialogue between

vaccine manufacturers, regulators and governments and will help address risk-benefit considerations by the WHO Global Advisory Committee on Vaccine Safety (GACVS) as well as policy-related recommendations by the WHO Strategic Advisory Group of Experts on Immunization (SAGE).

The consultation was chaired by Dr. Rick Bright and presentations were made by Drs. Arnold Monto, Rick Bright (on behalf of Dr. Larisa Rudenko) and Kathleen Coelingh to provide a background overview of the development and clinical experience of LAIV in both Russia and the USA. Accompanying slides are available for review.

## **Summary of presentations**

Live attenuated influenza vaccine development began more than 40 years ago following on the success of the polio vaccine. In early stages LAIV consisted mostly of a mixture of gene reassortments but later advent of molecular cloning enabled the introduction of specific mutations into a master host (donor) strain that could be retained as a backbone for the combination with surface HA and NA proteins, either by classical reassortment or reverse genetics methods. Two primary influenza A backbones were developed, one in Russia using A/Leningrad/134/57 and one in the USA using A/Ann Arbor/6/60, that are both attenuated and cold-adapted to grow well at reduced temperature such as that in the upper respiratory tract. LAIV have production advantages over traditional split virus vaccines reflected in high growth titers, higher production yield, lower cost and simplified purification. In addition, LAIV have potential immunological advantages over traditional split vaccines producing immunity similar to natural infection as reflected in the ability to elicit a broader immune response, triggering both humoral and cellular immunity that can be reflected in improved efficacy observed in clinical studies against matched and drifted viruses circulating in the community.

There have been extensive studies from numerous groups in the USA and Russia that have evaluated safety of LAIV and all studies showed little concern in terms of early reactogenicity. A large number of individuals have participated in over 126 clinical studies with LAIV developed in Russia and over 57 clinical studies with LAIV developed in the USA. Combined, these studies comprise a very large safety database that has accumulated over the years and has included large trials in children, adults and elderly populations. Solicited and adverse events in each study were mostly mild and transient upper respiratory and systemic symptoms. The most common adverse events in children were running nose or nasal congestion and low-grade fever.

Early reactogenicity was present in a limited number of individuals and it varied by study. In young adults there were symptoms of stuffy nose in about 10% to 20% of those evaluated. These symptoms were likely related to viral replication and were easily managed. Data from studies in the USA showed LAIV-induced wheezing in children less than 2 years of age, contributing to the licensure of the vaccine in this country down to age 2. However, this wheezing signal was weak in children between 12 and 24 months of age and strongest in children less than 12 months of age. There was an increased hospitalization rate in children 6 to 11 months of age and rates of medically significant wheezing were higher in LAIV vs. TIV (trivalent inactivated

vaccine) in children 6 to 23 months of age in a pre-specified analysis. These safety signals were not observed in children 24 to 59 months of age and there were no trends toward increased hospitalization in the older age group. In a risk/benefit analysis from a fairly mild seasonal influenza outbreak, there was positive benefit for children over 12 months of age to receive LAIV. In a pandemic situation, it is likely that the benefit ratio would be even greater in children down to 12 months of age and even younger. Limited data are available for children aged 6 months and below and additional studies in the age group are warranted for consideration for pandemic vaccine use.

Clinical studies from seasonal LAIV have shown that there is very high efficacy in young children. There may be a slightly lower level of efficacy seen in adults, compared to children, where there are pre-existing levels of antibodies to the vaccine strain for a given season. However, it is important to note that in the current pandemic situation with the novel H1N1 virus, data have shown that there is very little immunity in most of the population, likely indicating that LAIV would be highly efficacious in this scenario.

In children in the USA, efficacy was demonstrated in 6 placebo controlled studies. A higher efficacy of LAIV over TIV was observed in three TIV-controlled studies conducted during two different influenza seasons. Pivotal studies were conducted by Belshe et al in children 15 to 71 months of age showing over 93% (95% CI: 88, 96) efficacy against laboratory confirmed influenza against H3N2 and influenza B. Cross protection was also observed in the second year of the study when there was a major antigenic shift in the circulating from the vaccine strain of H3N2 virus. Interestingly, children who received the vaccine with an A/Wuhan-like virus yet had an efficacy rate of 86% (95% CI: 75, 92) against the major antigenically shifted A/Sydney-like virus that began circulating. Vaccine efficacy after the first dose of LAIV has been shown to be near 80% of the efficacy achieved after a second dose, indicating a high level of protection after the first dose of vaccine, while awaiting a second dose of vaccine to be administered.

Multiple safety and efficacy of LAIV studies have been conducted in adults. An efficacy in adults aged 60 years or older has shown a 53% and 42% reduction in culture-confirmed influenza cases against H3N2 and H1N1 influenza, respectively. Data have shown that LAIV can have reduced efficacy in healthy adults with antibody to previous influenza strains. Historically, in a year with a lot of drift, the vaccine may perform better in adults. In the current H1N1 outbreak, there is apparently no antibody in the population at large, so this issue should not be a concern. Most of the population should be susceptible to the novel H1N1 virus; therefore the LAIV should be highly efficacious and have potential to require only a single dose of the monovalent vaccine.

## **Discussion**

In general, it was agreed that LAIV could be a safe and effective intervention for the current H1N1 pandemic. There are advantages of using LAIV over injectable IIV that must be considered. LAIV are easy to produce in large quantities, are available in various formulations and administration is very easy with a needle-free advantage. They have the potential of achieving immunity following a single dose of vaccine. It

was estimated that three children could be vaccinated with a nasal vaccine in the time required to vaccinate one child with an injection. It was agreed that it is important to obtain clinical experience with the novel H1N1 LAIV to indicate that immunogenicity is similar to other influenza virus strains. In light of numerous potential advantages, experts on the consultation reviewed the following theoretical concerns:

### **Use of LAIV in children under 2 years of age**

Most of the discussion focused on general safety of using LAIV in specific populations. The primary safety concern was for the use of LAIV in children under 12 months of age. Due to clear wheezing and increased hospitalizations observed in previous studies with seasonal LAIV in this age group, great caution and reservation was raised about administering LAIV to children less than 12 months. However, it was also emphasized that the current pandemic situation may offer opportunity to further evaluate this issue in relatively large clinical trials. While there have been wheezing signals in children 12 to 24 months old, it was agreed that these signals have been generally weak and children in this age group LAIV could be considered if monitored carefully.

### **Special populations and contraindications**

In additions to restrictions placed on the use of LAIV in children under 12 months of age, the experts discussed potential use of LAIV in pregnant women, immune-compromised people, and in children with asthma. Several small studies have been conducted to evaluate the safety and efficacy in these populations, however data a limited and caution is warranted. It was agreed that as a precautionary measure LAIV should not be used in pregnant women, but could be considered carefully in any immune-compromised person with close monitoring. In general, it was suggested that application in populations over 12 months of age, without upper age limit, with contraindications similar as those listed on the FluMist package insert would serve as a good guideline for such pandemic LAIV for H1N1. It was noted that populations vaccinated and contraindications have some dependence on a risk/benefit balance to determine the risk of the vaccine compared to the severity of disease. For a pandemic, careful surveillance is warranted and if the virus is particularly pathogenic a new risk/benefit assessment may warrant reconsideration of contraindications.

The importance of post-marketing surveillance was also emphasized to be able to carefully monitor for any safety signals in all age groups and special populations. In addition, it might be important to advise countries planning to use LAIV to also have a supply of IIV for those populations for which LAIV might be contraindicated.

### **Genetic stability/viral shedding**

Studies have shown LAIV to be genetically stable with very little chance of reversion to a wildtype virus genotype. Unlike poliovirus, both the Russian and US backbone are genetically stable due to numerous mutations in several gene segments. It is important to note that both master virus backbones (from Russia and the USA) are derived from an H2N2 influenza virus and that current H3N2 and H1N1 strains have evolved from H2N2, sharing many internal genes with close identity.

It is thought that consequences of reassortment between a LAIV corresponding to the novel A(H1N1) pandemic strain with a wildtype seasonal strain would be no different than a reassortment between a wildtype H1N1 with a seasonal strain. This came up early in pandemic discussion groups concerning the use of LAIV in advance of a pandemic. Given the current widespread prevalence of the H1N1 virus, reassortment with a LAIV is of little concern. There is extensive experience with the common backbone that is used every year and the HA and NA are what is currently widespread in many countries around the world.

Shedding of the virus has been detected in swabs collected up to 11 days post-vaccination. However, the peak virus titer being shed occurred by day three and the titer shed was inversely related to the age of the subject. Therefore, the duration and magnitude of virus shedding was higher in children than adults. It is important to note that the peak titer of virus shed in children was rarely high enough to be infectious if transmitted to another person. Transmission of the vaccine virus strain has been documented in only a single child when LAIV was used in a daycare setting in Finland, though 80% of the children were shedding the vaccine virus. It is important to note that the virus that was transmitted was still genetically stable with no reversion or change from the temperature-sensitive/cold-adapted phenotype following transmission. The transmission probability from this study could be calculated to be 0.58%.

### **Delivery of pandemic LAIV**

There may be a significant shortage of spray devices and tips used for nasal delivery of pandemic LAIV. For example, MedImmune has potential to produce up to 160 million bulk doses of H1N1 vaccine by the end of the year, yet there are only approximately 40 million spray devices available. It is important to consider alternate delivery devices and methods to be able to accommodate the flux of bulk LAIV that will be produced by several manufacturers by the end of the year.

In US NIAID-sponsored studies from 1976 to 1995, over 8,000 children and adults from 2 months to 100 years of age were administered LAIV by nasal drops with the head tilted back. The formulation and volume was different than the current vaccine and various dosages were studied. Two large placebo/TIV controlled, multi-year efficacy studies in children and adults demonstrated that LAIV delivered by nasal drops were efficacious over a number of years studied. In addition, nasal drop vs nasal spray delivery was compared directly in a study by MedImmune, showing no statistical difference in HAI antibody titers.

In addition, some studies during early development with the Russian LAIV included administration by nose drops before advent of the spray device. Though not compared directly, there did not appear to be a notable reduction in the immune response after dropper administration compared to nasal spray, however data from such studies have not been published.

There are considerable data that support the use of drop delivery for LAIV, but there was concern about the possibility of having a vaccine like this administered in the same region by two different delivery methods. It will be important to offer the public some assurance that they are being offered equivalent vaccine. In addition, it is important to

consider the regulatory pathway necessary to approve use of alternate delivery methods. Carefully designed clinical studies will need to address these issues in the coming months.

### **Quality of eggs used for production of LAIV**

Although there was concern over a perception that regulatory agencies would require the use of SPF eggs for production of LAIV, there is known regulation in any of the countries where LAIV are licensed that requires the use of SPF eggs for the production of the vaccine. In the USA, MedImmune uses SPF eggs for production because this was part of manufacturing process that was submitted for licensure to the US FDA. Use of non-SPF eggs can therefore be considered, and the specification for production eggs needs to be evaluated on a case by case basis.

### **Summary**

A WHO virtual consultation was held with over 40 experts on regulatory, manufacturing, immunology, virology, clinical and policy to discuss the use of live attenuated influenza vaccines (LAIV) against the current H1N1 pandemic virus. Following overviews that highlighted numerous production, immunological and practical advantages of LAIV as well as the development and clinical experience of two licensed LAIV, one in Russia and one in the USA, participants discussed various topics related to the efficacy and safety of such vaccines and of their widespread use in mass vaccination campaigns against an H1N1 pandemic virus. While it was noted that LAIV were efficacious and safe in seasonal influenza vaccine formulations, clinical studies to show similar outcomes with the H1N1 vaccine were advised. The primary safety concern was the use of LAIV in children under 12 months of age, due to previously observed increases in hospitalization rates following vaccination. Theoretical concerns of potential reassortment, transmission and genetic stability of the vaccine virus strain were allayed with supporting data from numerous trials showing such incidences were extremely rare and would be of little consequence in the current pandemic situation when the virus is already widespread. It was also suggested that the target population be those over 12 months of age (without upper limit) and that general contraindications follow the licensed dossier that has been accepted in the USA for the MedImmune LAIV. While production is in progress in at least four different manufacturers, it was noted that there will be a shortage of spray delivery devices and alternative methods of nasal delivery such as drops should be evaluated. In general, it was agreed that LAIV can play a critical role in the current pandemic situation and should be considered a viable option with little concerns for safety in all but a few specified groups.

## List of Participants:

Norman Baylor (FDA USA)  
Robert Belshe (St Louis University USA)  
Supamit Chunsuttiwat (MOH Thailand)  
Kathleen Coelingh (MedImmuneUSA)  
Emer Cooke (EMEA United Kingdom)  
Nancy Cox (CDC USA)  
Pierre Demolis (EMEA France)  
Rajeev Dhere (SII, India)  
Kathryn Edwards (Vanderbilt University USA)  
Bruce Gellin (HHS USA)  
Hana Golding (FDA USA)  
Hector Izurieta (FDA USA)  
Veronika Jekerle (EMEA United Kingdom)  
Teena Jivapaisarnpong (FDA Thailand)  
Ruth Karron (Johns Hopkins School of Public Health USA)  
Alexander Klimov (US CDC)  
Igor Krasilnikov (Microgren, Russian Federation)  
Linda Lambert (NIAID USA)  
Barbara Law (Public Health Agency Canada)  
Roland Levandowski (Expert USA)  
Karen Midthun (FDA USA)  
Arnold Monto (University Michigan USA)  
Brian Murphy (UN NIH USA)  
Thomas Muster (AVIR Green Hills Biotec Austria)  
Elisa Pedone (EMEA United Kingdom)  
Eric Pelfrene (EMEA United Kingdom)  
Michael Perdue (HHS USA)  
Michael Pfeleiderer (Paul Ehrlich Institute, Germany)  
Punnee Pitisuttithum (Mahidol University Thailand)  
Gregory Poland (Mayo Clinic USA)  
Richard Richardson (EMEA United Kingdom)  
Robin Robinson (HHS USA)  
Stefania Salmaso (Istituto Superiore di Sanità Italy)  
Kanta Subbarao (NIH USA)  
Okubo Takayuki (Ministry of Health Japan)  
Sit Thirapakpoomanunt (GPO Thailand)  
Vinit Usavakidviree (FDA Thailand)  
Werawan Tangkeo (FDA Thailand)  
Prapassorn Thanaphollert (FDA Thailand)  
Klara Tiitso (EMEA United Kingdom)  
Timo Vesikari (University Tampere Finland)  
Bettie Voordouw (EMEA Netherlands)  
Jerry Weir (FDA USA)  
Lori Weiman (Medimmune USA)  
Suwit Wibulpolprasert (Ministry of Health Thailand)  
Peter Wright (Dartmouth Medical School USA)

## WHO Regions

Maureen Birmingham (WHO Representative Thailand)  
Florence Fuchs (WHO Lyon France)  
Gene Gavrilin (EURO Denmark)  
Robert Jensen (EURO Denmark)  
Shafiqul Hossain (WPRO Philippines)  
Hannah Kurtis (AMRO/PAHO USA)  
Houda Langar (EMRO)  
Deo Nshimirimana (AFRO Republic of Congo)  
Alba Maria Roperio (AMRO/PAHO USA)  
Arun Thapa (SEARO India)

## WHO Secretariat

Rick Bright (IVR)  
Peter Carrasco (EPI)  
Nicolas Collin (GIP)  
Martin Friede (IVR)  
Anne Huvos (GIP)  
Marie-Paule Kieny (IVR)  
Teresa Marengo (GIP)  
Laszlo Palkonyay (IVR)  
Dina Pfeifer (QSS)  
David Wood (QSS)  
Wenqing Zhang (GIP)  
Patrick Zuber (QSS)  
Florence Barthelemy (IVR)  
Ximena Laurie (IVR)