

## **Questions & Answers on the WHO-Nobilon Agreement for access to the LAIV TECHNOLOGY**

### **What is the epidemiological situation with H5N1 influenza viruses? (February 2, 2009)**

- **404 cases and 254 deaths** recorded since February 2003, **63 % case/fatality rate**
- **15 countries affected in 3 continents (Africa, Asia, Europe):** Azerbaijan, Bangladesh, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Lao People's Democratic Republic, Myanmar, Nigeria, Pakistan, Thailand, Turkey, Viet Nam
- **In 2008**, 44 cases with 33 deaths reported in 6 countries (Bangladesh, Cambodia, China, Indonesia, Myanmar, Viet Nam). Most cases are in countries where the disease in animals is already considered entrenched.

### **What is the Global Pandemic Influenza Action Plan to increase vaccine supply (GAP)?**

*In order to strengthen pandemic-influenza preparedness and response, the World Health Assembly requested the World Health Organization (WHO) Secretariat to seek solutions with international and national partners, including the private sector, to reduce the present global shortage of influenza vaccines for both epidemics and pandemics, including vaccination strategies that economize on the use of antigens, and development and licensing of antigen-sparing vaccine formulations. Following this request, the WHO held a consultation on 2-3 May 2006 in Geneva, Switzerland for the development of a "Global Pandemic Influenza Action Plan to Increase Vaccine Supply" (GAP) to identify the most promising approaches and strategies to increase availability of influenza pandemic vaccines.*

*Three strategic approaches are identified in the GAP:*

- *increase in seasonal vaccine use, leading to increased commercial demand for influenza vaccine with consequently increased production capacity*
- *increase in production capacity, independent of seasonal vaccine use*
- *research and development of novel broad spectrum influenza vaccines*

### **What is the latest progress on the GAP?**

*During the last two and half years a striking increase was observed in influenza vaccine production capacity. In addition to the huge investments of industrialized country vaccine manufacturers, six developing countries have shown progress as well towards developing domestic vaccine production capacity. Their effort has been supported by grants from the World Health Organization.*

*Some of the above 6 manufacturers, as well as other vaccine producers in developing countries have identified the LAIV technology as a most promising approach for supporting their national or regional pandemic influenza vaccine preparedness plans.*

### **What does LAIV mean?**

*LAIV stands for Live Attenuated Influenza Vaccine, which is administered intranasally.. The vaccine viruses are made "cold-adapted" and "temperature-sensitive", which means that the viruses can multiply and survive at lower temperatures and cannot survive at higher temperatures.*

### **How does LAIV work as a vaccine?**

*Because LAIV is "cold-adapted" and "temperature-sensitive", after intranasal application the vaccine viruses can temporarily survive at the lower temperatures in the nose but not at the higher temperatures in the lower respiratory tract. In this way the vaccine viruses can induce an immune response via the nose, but cannot cause illness through bronchitis or pneumonia. The LAIV viruses are safe and effective as vaccines; in brief LAIV vaccines mimic natural exposure while avoiding disease, but still inducing immunity against subsequent infection.*

**How are the LAIV vaccine viruses produced?**

*In the past wild-type viruses were passaged in eggs at lower temperature to make them “cold-adapted” and “temperature-sensitive”, resulting into attenuated so-called “Master-Donor-Strains” (MDS). The induced mutations that caused the attenuated phenotype in the MDS are in certain gene segments of the virus, but not in the gene segments that encode for the protective antigens H and N. By mixing the MDS with the wild-type virus against which protection by a vaccine is needed, and by applying the right selective environment (e.g. low temperature) the viruses are “re-assorted” into so-called “re-assortants” which have the attenuated safety features from the MDS and the protective antigens from the wild-type virus. Such an LAIV vaccine virus could be a cold-adapted and temperature-sensitive safe vaccine virus with protective antigens H1N1 or H3N2 for contemporary seasonal vaccine, or H5N1 for pandemic vaccine.*

**How is the vaccine produced?**

*Classically all Influenza vaccines are produced on fertilized eggs for virus multiplication. Subsequently the viruses are harvested and processed for vaccine formulation.*

**What are the advantages of LAIV compared to the currently available inactivated vaccines?**

*LAIV vaccines have at least three major advantages.*

*Firstly, the number of doses of LAIV which can be produced per egg are much higher than with inactivated vaccines. Especially in a pandemic situation this is considered to be a major advantage since more vaccine doses can come available in a shorter time.*

*Second, LAIV is administered in the nose through a very simple device, which will be much easier to put into practice on a large-scale by non-medically trained staff in case of a pandemic.*

*Third, since LAIV is mimicking natural infection more than injectable vaccines, it is expected that LAIV induces a more rapid and broader immune response. This may be of particular interest in pandemic situations.*

**The vaccine is administered through the nose. Is this new for vaccines?**

*The LAIV vaccine technology which is subject of this WHO licensing agreement, was developed in St Petersburg in Russia and the vaccine is already available in the Russian Federation since the 1970ties. Up to a total of approx. 100 million doses have since been applied successfully to all age groups during annual vaccination campaigns.*

*There is only one other intranasal influenza vaccine, which uses a similar technology. That vaccine was launched in the USA in 2003.*

**Can LAIV technology also be used in inter-pandemic situations?**

*Without a serious threat of e.g. an H5N1 pandemic, WHO does not currently recommend to apply an H5N1 influenza vaccine to the population. After formal declaration of a pandemic, LAIV might be used safely and effectively to limit disease and further spread of the pandemic.*

**What is the Intergovernmental process currently underway at WHO?**

*Under the overarching goal of Pandemic Influenza Preparedness, the intergovernmental process began in 2007 with a call by Member States to revise the network coordinated by WHO for sharing influenza viruses and resulting benefits. Among other goals, Member States seek greater equity in access to benefits resulting from the sharing of influenza viruses with pandemic potential. These benefits include vaccines, pharmaceuticals, transfer of technology and capacity building. Member States continue efforts to agree on*

*a Framework under which virus and benefit sharing will be more transparent, fairer and more equitable.*

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**About Schering-Plough & Nobilon**

*Nobilon is the human vaccine business unit of Schering-Plough's and combines activities in field of research, development and commercialization of human vaccines. Its head office is based in Boxmeer, The Netherlands. Nobilon was established in 2003. Nobilon has several development programmes in the pre-clinical stage. No product has as yet been marketed, Nobilon's live Attenuated Influenza Vaccine (LAIV) based on cell-culture is expected to enter the clinic for phase I studies in the first half of 2009.*

**About the World Health Organization (WHO)**

*The World Health Organization was founded in 1948. WHO is a public international organization consisting of 193 Member States, and a specialized agency of the United Nations. WHO is the directing and coordinating authority on international health work, and promotes technical cooperation for health, carries out programs to control and eradicate disease and strives to improve the quality of human life.*