3rd International Conference on Influenza and Zoonotic Diseases August 21-22, 2017 Birmingham, UK- Live influenza vaccines based on the cold-adapted master donor virus which were developed in Russia against avian influenza viruses of various subtypes

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Abstract

Statement of the Problem: Avian influenza viruses may transmit sporadically to humans possess continuous pandemic threat. As part of an influenza pandemic preparedness program, the WHO analyses a range of zoonotic and potentially pandemic influenza viruses for the development of appropriate vaccines. The cold-adapted A/Leningrad/134/17/57 (H2N2) (Len/17) master donor strain (MDS) is licensed in the Russian Federation for the production of the influenza A live influenza vaccine (LAIV) strains for the immunization of adults and children from 3 years old. Methodology & Theoretical Orientation: we used classical genetic reassortment to generate Len/17-based vaccine strains containing the surface antigens of the nonpathogenic avian influenza viruses of H5, H7, H9, H6 subtypes. Findings: All vaccine viruses were similar to parent MDS virus in term of replication in upper and lower respiratory tract of mice and fails to infect brain. In mice, the LAIV of H5N2, H7N3, and H9N2 subtypes provided protection against reinfection with distant. The H5N2 LAIV protected mice against reinfection with highly pathogenic H5N1 viruses, which differ significantly both antigenically and genetically, and H7N3 LAIV provided protection against H7N9. Protection against lethality and systemic spread of infection correlated with the formation of cross-reacting serum and secretory antibodies. On the model of post-Influenza bacterial pneumonia, the LAIV administration demonstrated a positive effect both on the decreasing the infecting virus reproduction in the respiratory tract of mice and on the removal of infectious streptococci. Also, H7N3 LAIV provided early protection against H7N9 infection. The H7N3 and H5N2 vaccine candidates demonstrated inability to reproduce in chickens, which confirms the safety of their production and use in areas with highly developed agriculture. In ferrets, the immunogenicity and protective efficacy of H7N3 LAIV were also demonstrated. Inoculation of H7N3 LAIV in ferrets did not cause any inflammation or destructive changes in lungs. When tested in clinical trials, the vaccine strains of H5N2 and H7N3 subtypes have shown high immunogenicity inducing the seroconversions of serum and local antibodies after double immunization. Conclusion & Significance: The Len/17-based vaccine strains obtained using classical reassortment in chick eggs with potentially pandemic subtypes as a source of surface antigens demonstrated cold-adaptation and attenuation. The use of LAIV can be effective against highly pathogenic influenza viruses even in the case of incomplete antigenic correspondence between the vaccine virus and the infectious strain.

Introduction:

Influenza viruses belong to the family Orthomyxoviridae. These are RNA-containing viruses possessing a negative fragmented genome. To date, there are four types (serotype) of influenza viruses—influenza A, B, C, and D. Influenza A viruses affect humans and a wide range of mammals (horses, pigs, dogs, wild and domestic cats, seals, ferrets) and birds (chickens, wild waterfowl, gulls, etc.). Only influenza A viruses are known as causative agents of severe epidemics and pandemics. The antigenic properties of influenza A viruses are based on two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA). Wild waterfowl are considered as a natural reservoir of influenza A viruses which is characterized by high divergence. The 16 HA subtypes and nine NA subtypes were detected in migratory waterfowl and poultry. Sometimes, avian influenza viruses overcome the interspecies barrier and infect poultry and mammals. Avian influenza viruses of subtypes H5N1, H7N3, H7N7, H7N9, and H9N2 may become pathogenic for humans and occasionally cause very severe infections. As part of an influenza pandemic preparedness program, the World Health Organization (WHO) analyzes a range of zoonotic and potentially pandemic influenza viruses for the development of appropriate vaccines as seasonal influenza vaccination does not protect against pandemic avian influenza viruses.

Avian influenza in humans; Most avian viruses are initially low virulent for birds, causing only transient asymptomatic intestinal infections in wild waterfowl. Viruses of subtypes H5 and H7 can be widespread among poultry, while acquiring the increased pathogenicity. This was observed during outbreaks caused by H5N2 viruses in 1983 or 1994–1995 in North America, subtype H7 (H7N7 or H7N2)—in Europe and in Australia. For the first time, “bird plague,” a disease caused (as is now known) by highly pathogenic influenza viruses, was described in 1878 during an outbreak among chickens in Italy. The outbreak causative agent was isolated in 1902 (virus A/Chicken/Brescia/1902 (H7N7)).

During similar outbreaks, repeatedly observed in Europe and around the world, several other viruses of H7 subtype were isolated. In 1955, those viruses were identified as belonging to a group of influenza viruses. The first of the highly pathogenic (HP) viruses of the H5N3 subtype—the A/Tern/South Africa/61—was isolated in 1961. HP avian influenza viruses can cause a mass death of chickens in a short time as a result of dissemination of infection in poultry with rapidly progressive neurologic symptoms, diarrhea, and fatal outcome. Until 1997, there was no obvious evidence of direct infection of humans with avian viruses. Nevertheless, serological studies revealed the presence of antibodies against avian viruses of various subtypes in human sera in southern China, Hong Kong, and East Asia, indicating exposure of some people to avian influenza viruses.

Development of live influenza vaccines against potentially pandemic avian influenza

The LAIVs preparation against potentially pandemic avian influenza viruses is conducted in two directions: the preparation of vaccine strains using classical genetic reassortment in chick embryos or through reverse genetics (RG) technique. The first attenuated A/Ann Arbor/6/60 (H2N2)-based vaccine strains were obtained by reverse genetics shortly after H5 influenza outbreaks in Hong Kong in 1997.

Conclusions

The use of non-pathogenic avian viruses as a source of surface antigens combined with the use of cold-adapted “donors” of attenuation can be a significant advantage in the development of vaccine strains for LAIV against potentially pandemic influenza using classical genetic reassortment in CE. Low pathogenic avian influenza viruses do not contain a polybasic amino acid insertion in the cleavage site and therefore do not require modification by reverse genetics methods prior to reassortment.

Note: This work is partially presented at 3rd International Conference on Influenza and Zoonotic Diseases Live influenza vaccines based on the cold-adapted master donor virus which were developed in Russia against avian influenza viruses of various subtypes on August 21-22, 2017.