

## **Development Of Human Influenza H5N1 Vaccines In Japan: Research And Clinical Trials**

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To develop human H5N1 influenza vaccine, Ministry of Health, Japan has organized a national project team with core members from the Ministry of Health, Labour and Welfare, National Pharmaceutical and Medical Device Agency, National Institute of Infectious Diseases, and four domestic vaccine manufactures. Since we experienced a low immunogenic property in humans of test vaccines derived from A/Hong Kong/156/97(H5N1), the project aimed to develop a prototype pandemic vaccine with highly immunogenic and to spare antigens to provide larger population with the vaccines. The WHO prototypes H5N1 vaccine strain, NIBRG-14, propagated in eggs was purified and fixed with formalin. Since addition of alum-adjuvant, the only adjuvant licensed in Japan, was shown to enhance the immunogenicity in animal models, alum-adjuvanted, inactivated whole virus vaccines were prepared. In pre-clinical studies, the test vaccines were shown to meet all safety requirements and to be higher immunogenic than non-adjuvanted vaccines. Then, phase 1 clinical studies were conducted with varied antigenic contents, 1.75, 5, and 15 mcg HA/dose in one or two doses, subcutaneously or intramuscularly. Preliminary results indicated the vaccine with 15 mcg HA was tolerable and did not cause severe adverse event. Serum antibody responses, assayed by hemagglutination inhibition test using horse red blood cells and micro-neutralizing test, were induced to an extent, though not extensively, by two shots with the medium or high dose of the vaccine preparation, meeting the international criteria. These results suggested that the inactivated whole virus vaccine conjugated with alum adjuvant is a practical formulation of H5N1 pandemic vaccines. This will save antigen contents and therefore make it possible to provide neighboring countries with more vaccines in case of pandemic influenza. Phase 2+3 clinical studies are now in progress.

Vaccines for Viral Infections in Developing Countries