

4 August 2009

*This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.*

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## **Chem-Bio News – Pandemic Influenza Edition #72**

**1. MILITARY PLANNING FOR POSSIBLE H1N1 OUTBREAK:** *"The U.S. military wants to establish regional teams of military personnel to assist civilian authorities in the event of a significant outbreak of the H1N1 virus this fall, according to Defense Department officials."*

**2. AGE-PRIORITIZED USE OF ANTIVIRALS DURING AN INFLUENZA PANDEMIC:** *"A model of influenza transmission and treatment suggests that, if the current swine flu pandemic behaves like the 1918 flu, antiviral treatment should be reserved for the young."*

**3. INCORPORATION OF MEMBRANE-BOUND, MAMMALIAN-DERIVED IMMUNOMODULATORY PROTEINS INTO INFLUENZA WHOLE VIRUS VACCINES BOOSTS IMMUNOGENICITY AND PROTECTION AGAINST LETHAL CHALLENGE:** *"This technology has broad applications in current influenza virus vaccine development and may prove particularly useful in boosting immune responses in the elderly, where current vaccines are minimally effective."*

**4. RANDOMIZED, DOUBLE-BLIND CONTROLLED PHASE 3 TRIAL COMPARING THE IMMUNOGENICITY OF HIGH-DOSE AND STANDARD-DOSE INFLUENZA VACCINE IN ADULTS 65 YEARS OF AGE AND OLDER:** *"These results suggest that the high-dose vaccine may provide improved protective benefits for older adults."*

**5. PROTECTIVE IMMUNITY TO INFLUENZA: LESSONS FROM THE VIRUS FOR SUCCESSFUL VACCINE DESIGN:** *"The paper under evaluation here introduces the notion that activation of caspase-1 inflammasomes in the hematopoietic cells in vivo are required for the establishment of Th1, cytotoxic T-lymphocyte and IgA responses to influenza virus infection.."*

**6. NATURAL ANTIBODY TO CONSERVED TARGETS OF HAEMOPHILUS INFLUENZAE LIMITS COLONIZATION OF THE MURINE NASOPHARYNX:** *"The broad effect of natural IgG against genetically diverse isolates suggests the presence of conserved species-wide protective targets of antibody."*

**7. PACKAGING, NOT YIELD, MAY BE PROBLEM FOR NASAL-SPRAY H1N1 VACCINE:** *"While most vaccine manufacturers have reaped below-average crops of H1N1 influenza vaccine virus from the eggs in which they're grown, MedImmune Inc. has a different problem: high virus yields, but a potential shortage of the devices used to spray the vaccine into the nose."*

**8. HHS ADVISORY PANEL TO MEET BY PHONE AND IN PERSON:** *"The National Biodefense Science Board, an advisory group that provides advice on chemical, biological, nuclear and radiological agents, will hold three public conference calls in August, October and November to discuss "Novel Influenza A H1N1," according to a notice in the Federal Register on July 31."*

# **CB Daily Report**

**Chem-Bio News**

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## **MILITARY PLANNING FOR POSSIBLE H1N1 OUTBREAK**

By Barbara Starr

CNN

July 28, 2009

“The U.S. military wants to establish regional teams of military personnel to assist civilian authorities in the event of a significant outbreak of the H1N1 virus this fall, according to Defense Department officials.

The proposal is awaiting final approval from Defense Secretary Robert Gates.

The officials would not be identified because the proposal from U.S. Northern Command's Gen. Victor Renuart has not been approved by the secretary.

The plan calls for military task forces to work in conjunction with the Federal Emergency Management Agency. There is no final decision on how the military effort would be manned, but one source said it would likely include personnel from all branches of the military.”

The full article can be found at: <http://www.cnn.com/2009/US/07/28/military.swine.flu/index.html>

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## **AGE-PRIORITIZED USE OF ANTIVIRALS DURING AN INFLUENZA PANDEMIC**

MedicalNews.net

July 27, 2009

“A model of influenza transmission and treatment suggests that, if the current swine flu pandemic behaves like the 1918 flu, antiviral treatment should be reserved for the young.

Researchers writing in the open access journal BMC Infectious Diseases found that, in this situation, providing the elderly with antiviral drugs would not significantly reduce mortality, and may lead to an increase in resistance.

Stefano Merler, from the Bruno Kessler Foundation, an Italian research organization, worked with researchers from the Istituto Superiore di Sanità to model the effect of antiviral treatment on the spread of influenza. He said, "Although it is too early to confidently predict some important features of the ongoing influenza pandemic, the use of antivirals is confirmed to be the most effective single intervention, in the absence of vaccines. It requires, however, a very large stockpile of antiviral drugs. Our work demonstrates that even in countries where the antiviral stockpile is not sufficient to treat 25% of the population, the minimum level suggested by the WHO, it is possible to reduce morbidity and excess mortality by prioritizing the use of antivirals by age".

The full article can be found at: <http://www.news-medical.net/news/20090727/Age-prioritized-use-of-antivirals-during-an-influenza-pandemic.aspx>

The original article can be found at: <http://www.biomedcentral.com/bmcinfectdis/>

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## **INCORPORATION OF MEMBRANE-BOUND, MAMMALIAN-DERIVED IMMUNOMODULATORY PROTEINS INTO INFLUENZA WHOLE VIRUS VACCINES BOOSTS IMMUNOGENICITY AND PROTECTION AGAINST LETHAL CHALLENGE**

Biotech Law Weekly

August 7, 2009

"Influenza epidemics continue to cause morbidity and mortality within the human population despite

widespread vaccination efforts. This, along with the ominous threat of an avian influenza pandemic (H5N1), demonstrates the need for a much improved, more sophisticated influenza vaccine."

"We have developed an in vitro model system for producing a membrane-bound Cytokine-bearing Influenza Vaccine (CYT-IVAC). Numerous cytokines are involved in directing both innate and adaptive immunity and it is our goal to utilize the properties of individual cytokines and other immunomodulatory proteins to create a more immunogenic vaccine. We have evaluated the immunogenicity of inactivated cytokine-bearing influenza vaccines using a mouse model of lethal influenza virus challenge. CYT-IVACs were produced by stably transfecting MDCK cell lines with mouse-derived cytokines (GM-CSF, IL-2 and IL-4) fused to the membrane-anchoring domain of the viral hemagglutinin. Influenza virus replication in these cell lines resulted in the uptake of the bioactive membrane-bound cytokines during virus budding and release. In vivo efficacy studies revealed that a single low dose of IL-2 or IL-4- bearing CYT-IVAC is superior at providing protection against lethal influenza challenge in a mouse model and provides a more balanced Th1/Th2 humoral immune response, similar to live virus infections. We have validated the protective efficacy of CYT-IVACs in a mammalian model of influenza virus infection."

"This technology has broad applications in current influenza virus vaccine development and may prove particularly useful in boosting immune responses in the elderly, where current vaccines are minimally effective."

The full article can be found at: (A.S. Herbert, et. al., "Incorporation of membrane-bound, mammalian-derived immunomodulatory proteins into influenza whole virus vaccines boosts immunogenicity and protection against lethal challenge". Virology Journal, 2009;6():42). Link not available.

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### **RANDOMIZED, DOUBLE-BLIND CONTROLLED PHASE 3 TRIAL COMPARING THE IMMUNOGENICITY OF HIGH-DOSE AND STANDARD-DOSE INFLUENZA VACCINE IN ADULTS 65 YEARS OF AGE AND OLDER**

Biotech Law Weekly

August 7, 2009

"A multicenter, randomized, double-blind controlled study was conducted to compare HD vaccine (which contains 60 mu g of hemagglutinin per strain) with the licensed standard-dose (SD) vaccine (which contains 15 mu g of hemagglutinin per strain) in adults  $\geq$  65 years of age. HD vaccine was administered to 2575 subjects, and SD vaccine was administered to 1262 subjects. There was a statistically significant increase in the rates of seroconversion and mean hemagglutination inhibition titers at day 28 after vaccination among those who received HD vaccine, compared with those who received SD vaccine. Mean postvaccination titers for individuals who received HD vaccine were 116 for H1N1, 609 for H3N2, and 69 for B strain; for those who received SD vaccine, mean postvaccination titers were as 67 for H1N1, 333 for H3N2, and 52 for B strain. The HD vaccine met superiority criteria for both A strains, and the responses for B strain met noninferiority criteria. Seroprotection rates were also higher for those who received HD vaccine than for those who received SD vaccine vaccine, for all strains. Local reactions were more frequent in individuals who received HD vaccine, but the reactions were mild to moderate. There was a statistically significant increase in the level of antibody response induced by HD influenza vaccine, compared with that induced by SD vaccine, without an attendant increase in the rate or severity of clinically relevant adverse reactions."

"These results suggest that the high-dose vaccine may provide improved protective benefits for older adults."

The full article can be found at: (A.R. Falsey, et. al., "Randomized, Double-Blind Controlled Phase 3 Trial Comparing the Immunogenicity of High-Dose and Standard-Dose Influenza Vaccine in Adults 65 Years of Age and Older", Journal of Infectious Diseases, 2009;200(2):172-180). Link not available.

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## **PROTECTIVE IMMUNITY TO INFLUENZA: LESSONS FROM THE VIRUS FOR SUCCESSFUL VACCINE DESIGN**

Biotech Law Weekly  
August 7, 2009

"In particular, mucosal and T-cell-mediated immunity may offer a more cross-reactive vaccine approach for the prevention of epidemic or potentially pandemic influenza. Thus, it is imperative to more fully understand the molecular events that occur in the host upon infection with a live virus and, in particular, to better evaluate the role of the distinct signaling pathways involved in developing protective immune responses."

"The paper under evaluation here introduces the notion that activation of caspase-1 inflammasomes in the hematopoietic cells in vivo are required for the establishment of Th1, cytotoxic T-lymphocyte and IgA responses to influenza virus infection.."

The full article can be found at: (B. Garulli, et. al., "Protective immunity to influenza: lessons from the virus for successful vaccine design". Expert Review of Vaccines, 2009;8(6):689-693). Link not available.

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## **NATURAL ANTIBODY TO CONSERVED TARGETS OF HAEMOPHILUS INFLUENZAE LIMITS COLONIZATION OF THE MURINE NASOPHARYNX**

Biotech Law Weekly  
August 7, 2009

"Therefore, we investigated host factors involved in limiting H. influenzae colonization in BALB/c mice, as colonization can be established in this genetic background. Unlike what is observed in the C57BL/6 background, initial colonization of BALB/c mice was mainly limited by adaptive immune components. This effect on colonization did not require either CD4- or CD8-positive T cells. Instead, initial colonization by genetically diverse strains was limited by preexisting natural antibody with a lesser contribution of complement activity and the presence of neutrophils. Natural serum immunoglobulin from mice was able to bind to the bacterial surface and exhibited complement-dependent bactericidal activity against these genetically diverse H. influenzae strains. Moreover, natural immunoglobulin G (IgG) recognizing these strains was detected at the nasopharyngeal mucosal surface. This antibody-mediated effect required exposure to the normal mouse microbial flora, since mice raised under germfree (GF) conditions showed increased levels of H. influenzae colonization that were not limited by adaptive immunity. In addition, serum IgG from GF mice exhibited less surface binding to H. influenzae, suggesting that natural antibody, induced through prior exposure to the microbial flora, mediated the observed reduction in initial colonization."

"The broad effect of natural IgG against genetically diverse isolates suggests the presence of conserved species-wide protective targets of antibody."

The full article can be found at: (T.A. Zola, et. al., "Natural antibody to conserved targets of Haemophilus influenzae limits colonization of the murine nasopharynx". Infection and Immunity, 2009;77(8):3458-65). Link not available.

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## **PACKAGING, NOT YIELD, MAY BE PROBLEM FOR NASAL-SPRAY H1N1 VACCINE**

By Robert Roos  
CIDRAP News - Center for Infectious Disease Research & Policy (University of Minnesota)  
July 30, 2009

"While most vaccine manufacturers have reaped below-average crops of H1N1 influenza vaccine virus from the eggs in which they're grown, MedImmune Inc. has a different problem: high virus yields, but a

potential shortage of the devices used to spray the vaccine into the nose.

The company has produced more than 20 million bulk doses of the vaccine, well above the 12.8 million ordered so far by the US government, and has the capacity to make 205 million bulk doses, said Ben Machielse, executive vice president of operations, in an interview this week.

But he said the company has the capability to put only 41 million doses in sprayers, so it is looking into the possibility of using droppers instead—an option that would require additional regulatory review but may permit making more vaccine available sooner. The Maryland-based company, part of AstraZeneca, makes the seasonal vaccine FluMist, which uses a live but weakened virus.”

The full article can be found at:

<http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/jul3009medimmune.html>

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## **HHS ADVISORY PANEL TO MEET BY PHONE AND IN PERSON**

Government Security News

August 03, 2009

“The National Biodefense Science Board, an advisory group that provides advice on chemical, biological, nuclear and radiological agents, will hold three public conference calls in August, October and November to discuss “Novel Influenza A H1N1,” according to a notice in the Federal Register on July 31.”

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“The public conference calls will take place on Aug. 14, Oct. 14 and Nov. 13, each running from 12 noon until 2:00 PM (Eastern time). Further information about these conference calls is available from , of the National Biodefense Science Board.”

The full article can be found at: <http://www.gsnmagazine.com/cms/features/news-analysis/2433.html>

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