

14 July 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 #69**

**1. IMMUNOGENICITY OF HEMAGGLUTININ FROM A/BAR-HEADED GOOSE/ QINGHAI/1A/05 AND A/ANHUI/1/05 STRAINS OF H5N1 INFLUENZA VIRUSES PRODUCED IN NICOTIANA BENTHAMIANA PLANTS:** *“These results Suggest the Utility of our plant-expression system for recombinant influenza vaccine production.”*

**2. MICRORNA-MEDIATED SPECIES-SPECIFIC ATTENUATION OF INFLUENZA A VIRUS:** *“This approach might be combined with existing LAIVs to increase attenuation and improve vaccine safety.”*

**3. SEBELIUS EXPECTS LAUNCH OF H1N1 VACCINATION DRIVE IN FALL:** *“If an effective vaccine for pandemic H1N1 influenza is available, the federal government expects to mount an H1N1 vaccination campaign this fall, initially targeting schoolchildren, adults with health problems, pregnant women, and healthcare and emergency workers, a top US official said today.”*

**4. PHYSICOCHEMICAL AND IMMUNOLOGICAL CHARACTERIZATION OF N,N,N-TRIMETHYL CHITOSAN-COATED WHOLE INACTIVATED INFLUENZA VIRUS VACCINE FOR INTRANASAL ADMINISTRATION:** *“Coating of WIV with TMC is a simple procedure to improve the delivery and immunogenicity of i.n. administered WIV and may enable effective i.n. vaccination against influenza..”*

**5. VIRAL LOADS AND DURATION OF VIRAL SHEDDING IN ADULT PATIENTS HOSPITALIZED WITH INFLUENZA:** *“On the basis of our findings, areas of further research regarding the management of patients hospitalized with influenza should include clinical trials on delayed antiviral therapy in compromised and seriously ill patients [16, 39, 48], the use of a higher•dose regimen (eg, 150 mg oseltamivir twice daily), a more prolonged course of treatment (>5 days) [14, 16, 39, 48], the risk of emergence of antiviral resistance [44, 48, 49], the role of rapid diagnostic tests in different clinical settings (test performances can be affected by viral load and specimen type) [7, 24, 26, 35–38, 50], the adequacy of currently recommended infection control measures [29, 40, 41], and viral kinetics of other influenza virus subtypes (eg, H1N1). Such information is important for influenza pandemic preparedness [1, 39, 41].”*

## **6. OBAMA ADMINISTRATION CALLS ON NATION TO BEGIN PLANNING AND PREPARING FOR FALL FLU SEASON & THE NEW H1N1 VIRUS:**

*"Administration Leaders Say that Flu Preparedness is a "Shared Responsibility" Announce New Funding for States and New Nation-Wide Flu Prevention Campaign at flu.gov."*

**7. STUDY: SWINE FLU RESEMBLES 1918 VIRUS:** *"The new H1N1 influenza virus bears a disturbing resemblance to the virus strain that caused the 1918 flu pandemic, with a greater ability to infect the lungs than common seasonal flu viruses, researchers reported on Monday."*

**8. WHO SAYS NEW FLU "UNSTOPPABLE", CALLS FOR VACCINE:** *"Saying the new H1N1 virus is "unstoppable", the World Health Organization gave drug makers a full go-ahead to manufacture vaccines against the pandemic influenza strain on Monday and said healthcare workers should be the first to get one."*

**9. EXPERTS UNEARTH HISTORY OF PANDEMIC FLU VIRUSES:** *"Flu viruses that sparked the three worst pandemics in the last century circulated in their near-complete forms for years before the catastrophes occurred, researchers in Hong Kong and the United States have found."*

## **10. PANDEMIC FLU VACCINE YIELDS WORSE THAN EXPECTED. - JULY 13, 2009:**

*"Vaccine makers have told the WHO that the 'seed strains' grown to produce vaccine against the pandemic virus are giving poor yields of antigen."*

# CB Daily Report

## ***Chem-Bio News***

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### **IMMUNOGENICITY OF HEMAGGLUTININ FROM A/BAR-HEADED GOOSE/ QINGHAI/1A/05 AND A/ANHUI/1/05 STRAINS OF H5N1 INFLUENZA VIRUSES PRODUCED IN NICOTIANA BENTHAMIANA PLANTS**

Health Risk Factor Week

July 14, 2009

"Vaccination is the preferred strategy for the prevention and control Of influenza infections and the availability of a system for the rapid engineering and production of vaccines is required in the event of an influenza pandemic. In this study, we engineered and produced recombinant hemagglutinin (HA) from A/Bar-headed Goose/Qinghai/1A/05 (clade 2.2) and A/ Anhui/1/2005 (clade 2.3) in Nicotiana benthamiana Plants. Immunization of mice with these plant-derived HA antigens elicited serum hemagglutination inhibition (HI) and virus neutralization (VN) antibodies."

"These results suggest the utility of our plant-expression system for recombinant influenza vaccine production."

The full article can be found at: (Y. Shoji, et. al., "Immunogenicity of hemagglutinin from A/ Bar-headed Goose/Qinghai/1A/05 and A/Anhui/1/05 strains of H5N1 influenza viruses produced in Nicotiana benthamiana plants". Vaccine, 2009;27(25-26 Sp.): 3467-3470). Link

not available.

[Return to Top](#)

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## **MICRORNA-MEDIATED SPECIES-SPECIFIC ATTENUATION OF INFLUENZA A VIRUS**

Health Risk Factor Week

July 14, 2009

"Present prophylactic strategies focus on egg-grown, live, attenuated influenza vaccines (LAIVs), in which attenuation is generated by conferring temperature sensitivity onto the virus."

"Here we describe an alternative approach to attenuating influenza A virus based on microRNA-mediated gene silencing. By incorporating nonavian microRNA response elements (MREs) into the open-reading frame of the viral nucleoprotein, we generate reassortant LAIVs for H1N1 and H5N1 that are attenuated in mice but not in eggs. MRE-based LAIVs show a greater than two-log reduction in mortality compared with control viruses lacking MREs and elicit a diverse antibody response."

"This approach might be combined with existing LAIVs to increase attenuation and improve vaccine safety."

The full article can be found at: (J.T. Perez, et. al., "MicroRNA-mediated species-specific attenuation of influenza A virus". *Nature Biotechnology*, 2009;27(6):572-U117). Link not available.

[Return to Top](#)

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## **SEBELIUS EXPECTS LAUNCH OF H1N1 VACCINATION DRIVE IN FALL**

By Robert Roos

CIDRAP News (Center for Infectious Disease Research & Policy – University of Minnesota)

July 09, 2009

"If an effective vaccine for pandemic H1N1 influenza is available, the federal government expects to mount an H1N1 vaccination campaign this fall, initially targeting schoolchildren, adults with health problems, pregnant women, and healthcare and emergency workers, a top US official said today.

Health and Human Services (HHS) Secretary Kathleen Sebelius discussed the vaccination plans at the Obama administration's H1N1 Influenza Preparedness Summit, a one-day meeting designed to stimulate preparedness nationwide. The session drew about 500 state, tribal, and territorial health and education officials to Bethesda, Md., and was streamed over the Web.

"While we have made no final decisions about its scope, and have 'off ramps' built into our

decision making process if the circumstances change, at this point, we expect to initiate a voluntary fall vaccination program against the 2009 H1N1 flu virus," Sebelius said in her prepared remarks.

She commented that the risk of increased antiviral resistance in the H1N1 virus is a "serious consideration," underlining the importance of vaccination.

Sebelius said the current estimate is that some vaccine will be ready for distribution in mid-October."

The full article can be found at: <http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/jul0909summit-jw.html>

[Return to Top](#)

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## **PHYSICOCHEMICAL AND IMMUNOLOGICAL CHARACTERIZATION OF N,N,N-TRIMETHYL CHITOSAN-COATED WHOLE INACTIVATED INFLUENZA VIRUS VACCINE FOR INTRANASAL ADMINISTRATION**

Pharma Investments, Ventures & Law Weekly  
July 19, 2009

"The purpose of this study was the development and physicochemical and immunological characterization of intranasal (i.n.) vaccine formulations of whole inactivated influenza virus (WIV) coated with N,N,N-trimethyl chitosan (TMC). Synthesized TMCs with a degree of quarternization of 15% (TMC15) or 37% (TMC37) were tested in vitro for their ability to decrease the transepithelial resistance (TEER) of an epithelial cell monolayer."

"TMC15- and TMC37-coated WIV (TMC15-WIV and TMC37-WIV) were characterized by zeta potential measurements, dynamic light scattering, electron microscopy and gel permeation chromatography. Mice were vaccinated i.n. with selected vaccine formulations and immunogenicity was determined by measuring serum hemagglutination inhibition (HI) and serum IgG, IgG1 and IgG2a/c titers. Also a pulse-chase study with TMCs in solution administered i.n. 2 h prior to WIV was performed. Protective efficacy of vaccination was determined by an aerosol virus challenge. TMC37 induced a reversible decrease in TEER, suggesting the opening of tight junctions, whereas TMC15 did not affect TEER. Simple mixing of (negatively charged) WIV with TMC15 or TMC37 resulted in positively charged particles with TMCs being partially bound. Intranasal immunization with TMC37-WIV or TMC15-WIV induced stronger HI, IgG, IgG1 and IgG2a/c titers than WIV alone. TMC37-WIV induced the highest immune responses. Both TMC15-WIV and TMC37-WIV provided protection against challenge, whereas WIV alone was not protective. Intranasal administration of TMC prior to WIV did not result in significant immune responses, indicating that the immunostimulatory effect of TMC is primarily based on improved i.n. delivery of WIV."

"Coating of WIV with TMC is a simple procedure to improve the delivery and immunogenicity of i.n. administered WIV and may enable effective i.n. vaccination against influenza.."

The full article can be found at: (N. Hagens, et. al., "Physicochemical and Immunological Characterization of N,N,N-Trimethyl Chitosan-Coated Whole Inactivated Influenza Virus Vaccine for Intranasal Administration". *Pharmaceutical Research*, 2009;26(6):1353-1364). Link not available.

[Return to Top](#)

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## **VIRAL LOADS AND DURATION OF VIRAL SHEDDING IN ADULT PATIENTS HOSPITALIZED WITH INFLUENZA**

By Nelson Lee, Paul K. S. Chan, David S. C. Hui, Timothy H. Rainer, Eric Wong, Kin•Wing Choi, Grace C. Y. Lui, Bonnie C. K. Wong, Rita Y. K. Wong, Wai•Yip Lam, Ida M. T. Chu, Raymond W. M. Lai, Clive S. Cockram, and Joseph J. Y. Sung

*The Journal of Infectious Diseases*

July 09, 2009

### "Background.

The goal of this study was to characterize viral loads and factors affecting viral clearance in persons with severe influenza.

### Methods.

This was a 1•year prospective, observational study involving consecutive adults hospitalized with influenza. Nasal and throat swabs were collected at presentation, then daily until 1 week after symptom onset. Real•time reverse•transcriptase polymerase chain reaction to determine viral RNA concentration and virus isolation were performed. Viral RNA concentration was analyzed using multiple linear or logistic regressions or mixed•effect models.

### Results.

One hundred forty•seven inpatients with influenza A (H3N2) infection were studied (mean age  $\pm$  standard deviation, years). Viral RNA concentration at presentation positively correlated with symptom scores and was significantly higher than that among time•matched outpatients (control subjects). Patients with major comorbidities had high viral RNA concentration even when presenting  $>2$  days after symptom onset (mean  $\pm$  standard deviation, vs log<sub>10</sub> copies/mL; ;  $\beta$ , +0.86 [95% confidence interval, +0.03 to +1.68]). Viral RNA concentration demonstrated a nonlinear decrease with time; 26% of oseltamivir•treated and 57% of untreated patients had RNA detected at 1 week after symptom onset. Oseltamivir started on or before symptom day 4 was independently associated with an accelerated decrease in viral RNA concentration (mean  $\beta$  [standard error], -1.19 [0.43] and -0.68 [0.33] log<sub>10</sub> copies/mL for patients treated on day 1 and days 2–3, respectively; ) and viral RNA clearance at 1 week (odds ratio, 0.10 [95% confidence interval, 0.03–0.35] and 0.30 [0.10–0.90] for patients treated on day 1–2 and day 3–4, respectively). Conversely, major comorbidities and systemic corticosteroid use for asthma or chronic obstructive pulmonary disease exacerbations were associated with slower viral clearance. Viral RNA clearance was associated with a shorter hospital stay (7.0 vs 13.5 days; ).

Conclusion.

On the basis of our findings, areas of further research regarding the management of patients hospitalized with influenza should include clinical trials on delayed antiviral therapy in compromised and seriously ill patients [16, 39, 48], the use of a higher-dose regimen (eg, 150 mg oseltamivir twice daily), a more prolonged course of treatment (>5 days) [14, 16, 39, 48], the risk of emergence of antiviral resistance [44, 48, 49], the role of rapid diagnostic tests in different clinical settings (test performances can be affected by viral load and specimen type) [7, 24, 26, 35–38, 50], the adequacy of currently recommended infection control measures [29, 40, 41], and viral kinetics of other influenza virus subtypes (eg, H1N1). Such information is important for influenza pandemic preparedness [1, 39, 41].

Patients hospitalized with severe influenza have more active and prolonged viral replication. Weakened host defenses slow viral clearance, whereas antivirals started within the first 4 days of illness enhance viral clearance.”

The full article can be found at: <http://www.journals.uchicago.edu/doi/full/10.1086/600383?cookieSet=1>

[Return to Top](#)

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## **OBAMA ADMINISTRATION CALLS ON NATION TO BEGIN PLANNING AND PREPARING FOR FALL FLU SEASON & THE NEW H1N1 VIRUS**

US Department of Health and Human Services News Release  
July 09, 2009

“Obama Administration Calls on Nation to Begin Planning and Preparing for Fall Flu Season & the New H1N1 Virus

Administration Leaders Say that Flu Preparedness is a “Shared Responsibility” Announce New Funding for States and New Nation-Wide Flu Prevention Campaign at [flu.gov](http://flu.gov)

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“Over the course of coming weeks and months, we will move aggressively to prepare the nation for the possibility of a more severe outbreak of the H1N1 virus,” said HHS Secretary Sebelius. “We ask the American people to become actively engaged with their own preparation and prevention. It’s a responsibility we all share.”

“The federal government is working together with its federal, state, local and tribal partners to develop a nation-wide plan to combat the H1N1 flu that incorporates the lessons we learned this spring,” said Homeland Security Secretary Napolitano. “The H1N1 Summit will allow us to continue this aggressive preparation for all possible H1N1 virus outbreak scenarios to ensure that we are doing everything possible to keep our country safe and healthy.”

“Effectively dealing with a potential H1N1 outbreak requires all of us -- parents, educators, health providers, and local, state and federal governments -- working together on our emergency management plan,” said Education Secretary Duncan. “Today’s Flu Summit is an important step in that direction. Our primary goals at the Department of Education are the health and well being of students, faculty and staff, and ensuring that, in the event of any school closures, the learning process will continue. ”

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Throughout the one-day summit, Administration officials laid out specific ways that states and local governments could start their planning and preparation efforts and announced new programs and resources to help state and local governments, the medical community and every day America prepare for H1N1 and the fall flu season.

First, HHS will make available preparedness grants worth a total of \$350 million. These grants were funded by Congress in the latest supplemental appropriations bill and they will give state and local public health offices and health care systems valuable resources to step up their preparedness efforts.

Second, the federal government will centralize communications about H1N1 and seasonal flu on the federal government’s new Web site [www.flu.gov](http://www.flu.gov). This one-stop comprehensive site brings together flu-related information from across HHS and other federal agencies. The expanded site builds on the pandemic planning information long presented on [www.pandemicflu.gov](http://www.pandemicflu.gov), and incorporates information about the novel H1N1 flu as well as the seasonal flu.

Finally, HHS is launching a new PSA campaign contest to encourage more Americans to get involved in the nation’s flu preparedness efforts by making a 15-second or 30-second PSA. Officials at the summit stressed the idea of “shared responsibility” when it comes to combating the flu and the goal of the new HHS PSA campaign contest is to tap into the nation’s creativity to help educate Americans about how to plan for and prevent the spread of H1N1 influenza. HHS will evaluate submissions and will present the best PSAs back to the public so everyone can vote on their favorite submission. The winning PSA will receive \$2,500 in cash and will appear on national television. Contest details as well more information about the larger effort to plan and prepare for the flu season are available at [www.flu.gov](http://www.flu.gov).”

The full article can be found at: <http://www.hhs.gov/news/press/2009pres/07/20090709a.html>

[Return to Top](#)

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## **STUDY: SWINE FLU RESEMBLES 1918 VIRUS**

FoxNews.com  
July 13, 2009

“The new H1N1 influenza virus bears a disturbing resemblance to the virus strain that

caused the 1918 flu pandemic, with a greater ability to infect the lungs than common seasonal flu viruses, researchers reported on Monday.

Tests in several animals confirmed other studies that have shown the new swine flu strain can spread beyond the upper respiratory tract to go deep into the lungs — making it more likely to cause pneumonia, the international team said.

In addition, they found that people who survived the 1918 pandemic seem to have extra immune protection against the virus, again confirming the work of other researchers.

"When we conducted the experiments in ferrets and monkeys, the seasonal virus did not replicate in the lungs," said Yoshihiro Kawaoka of the University of Wisconsin, who led the study.

The H1N1 virus replicates significantly better in the lungs."

The full article can be found at: <http://www.foxnews.com/story/0,2933,532020,00.html>

[Return to Top](#)

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## **WHO SAYS NEW FLU "UNSTOPPABLE", CALLS FOR VACCINE**

By Maggie Fox

Reuters

July 14, 2009

"Saying the new H1N1 virus is "unstoppable", the World Health Organization gave drug makers a full go-ahead to manufacture vaccines against the pandemic influenza strain on Monday and said healthcare workers should be the first to get one.

Every country will need to vaccinate citizens against the swine flu virus and must choose who else would get priority after nurses, doctors and technicians, said Dr. Marie-Paule Kieny, WHO director of the Initiative for Vaccine Research.

Several reports showed the new virus attacks people differently than seasonal flu -- affecting younger people, the severely obese and seemingly healthy adults, and causing disease deep in the lungs."

The full article can be found at: <http://www.reuters.com/article/healthNews/idUSTRE56C60820090714>

[Return to Top](#)

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## **EXPERTS UNEARTH HISTORY OF PANDEMIC FLU VIRUSES**

By Tan Ee Lyn

Reuters

July 13, 2009

"Flu viruses that sparked the three worst pandemics in the last century circulated in their near-complete forms for years before the catastrophes occurred, researchers in Hong Kong and the United States have found.

The H1N1 virus that sparked the Spanish flu of 1918-1919 circulated in swine and humans well before the pandemic started, and it did not come directly from birds as previously thought, they added. Instead, it was probably generated by genetic exchanges between flu viruses from swine and humans.

This contrasts sharply with previous studies which suggested that the H1N1 virus of 1918 was a mutant that jumped direct from birds to human and ended up killing as many as 50 million people.

The findings are considered important because of the lack of studies of the virus in animals before the current outbreak of H1N1. Through understanding the natural history of viruses, monitoring of current viruses can be fine-tuned, the team from the University of Hong Kong and St Jude Children's Hospital in the United States wrote."

The full article can be found at: <http://www.reuters.com/article/scienceNews/idUSTRE56C64720090713>

[Return to Top](#)

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## **PANDEMIC FLU VACCINE YIELDS WORSE THAN EXPECTED. - JULY 13, 2009**

Nature.com

July 13, 2009

"Efforts to produce vaccine against the pandemic H1N1 2009 virus have run into problems. Vaccine makers have told the WHO that the 'seed strains' grown to produce vaccine against the pandemic virus are giving poor yields of antigen. The yield is a quarter to a half of that vaccine makers typically get for seasonal flu vaccine production. WHO has now started to try to make a new set of seed strains using new viral isolates – a process which will take around a month – in the hope that some perform better. But if improved yields aren't forthcoming, the amount of pandemic vaccine available from existing production plant capacity could be cut by half or more, whereas there already isn't enough to go round."

The full article can be found at: [http://blogs.nature.com/news/thegreatbeyond/2009/07/pandemic\\_vaccine\\_yields\\_worse.html](http://blogs.nature.com/news/thegreatbeyond/2009/07/pandemic_vaccine_yields_worse.html)

[Return to Top](#)

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