

25 May 2010

*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 #113**

- 1. GLOBAL PUBLIC HEALTH IMPLICATIONS OF A MASS GATHERING IN MECCA, SAUDI ARABIA DURING THE MIDST OF AN INFLUENZA PANDEMIC:** *"In 2008, 2.5 million pilgrims from 140 countries performed the Hajj. Pilgrims (1.7 million) were of international (non-Saudi) origin, of which 91.0% traveled to Saudi Arabia via commercial flights. International pilgrims (11.3%) originated from low-income countries, with the greatest numbers traveling from Bangladesh (50,419), Afghanistan (32,621), and Yemen (28,018)."*
- 2. POTENT VESICULAR STOMATITIS VIRUS-BASED AVIAN INFLUENZA VACCINES PROVIDE LONG-TERM STERILIZING IMMUNITY AGAINST HETEROLOGOUS CHALLENGE:** *"The vaccines provide complete protection against morbidity and mortality after heterologous challenge with clade 0 and clade 1 strains in animals even 1 year after vaccination. Postchallenge pulmonary virus loads show that these vectors provide sterilizing immunity."*
- 3. PB1-F2 EXPRESSION BY THE 2009 PANDEMIC H1N1 INFLUENZA VIRUS HAS MINIMAL IMPACT ON VIRULENCE IN ANIMAL MODELS:** *"In summary, our study demonstrates that PB1-F2 expression by the Cal/09 virus modulates the immune response to infection while having a minimal effect on virus virulence in two mammalian models."*
- 4. ALTERNATIVE LIVE-ATTENUATED INFLUENZA VACCINES BASED ON MODIFICATIONS IN THE POLYMERASE GENES PROTECT AGAINST EPIDEMIC AND PANDEMIC FLU:** *"In addition, our data provide evidence that the use of these alternative backbones could potentially circumvent the effects of original antigenic sin (OAS) in certain circumstances."*
- 5. ANTIGENIC AND GENETIC DIVERSITY OF HIGHLY PATHOGENIC AVIAN INFLUENZA A (H5N1) VIRUSES ISOLATED IN EGYPT:** *"The antigenic changes in Egyptian viruses isolated during 2007-08 necessitated that two of these strains be considered as potential H5N1 pre-pandemic vaccine candidates."*
- 6. DEVELOPMENT AND EVALUATION OF A ONE-STEP REAL-TIME RT-PCR ASSAY FOR UNIVERSAL DETECTION OF INFLUENZA A VIRUSES FROM AVIAN AND MAMMAL SPECIES:** *"Our results predicted that this RRT-PCR assay was able to detect 99.5% of known human IA virus strains, 99.84% of pandemic influenza A (H1N1) strains, 99.75% of avian strains, 98.89% of swine strains, 98.15% of equine strains, and 100% of influenza A viruses of other origin."*
- 7. MODELING HOST RESPONSES IN FERRETS DURING A/CALIFORNIA/07/2009 INFLUENZA INFECTION:** *"We propose that lung pathology in humans occurs during the innate phase of host immunity and a delay or failure to switch to the adaptive phase may contribute to morbidity and mortality during severe 2009-H1N1 infections."*

# **CB Daily Report**

## **Chem-Bio News**

## **DURING THE MIDST OF AN INFLUENZA PANDEMIC**

World Disease Weekly

May 11, 2010

"After the Hajj, resource-limited countries with large numbers of traveling pilgrims could be vulnerable, given their limited ability to purchase H1N1 vaccine and capacity to respond to a possible wave of H1N1 introduced via returning pilgrims. We studied the worldwide migration of pilgrims traveling to Mecca to perform the Hajj in 2008 using data from the Saudi Ministry of Health and international air traffic departing Saudi Arabia after the 2008 Hajj using worldwide airline ticket sales data. We used gross national income (GNI) per capita as a surrogate marker of a country's ability to mobilize an effective response to H1N1. In 2008, 2.5 million pilgrims from 140 countries performed the Hajj. Pilgrims (1.7 million) were of international (non-Saudi) origin, of which 91.0% traveled to Saudi Arabia via commercial flights. International pilgrims (11.3%) originated from low-income countries, with the greatest numbers traveling from Bangladesh (50,419), Afghanistan (32,621), and Yemen (28,018). Nearly 200,000 pilgrims that performed the Hajj in 2008 originated from the world's most resource-limited countries, where access to H1N1 vaccine and capacity to detect and respond to H1N1 in returning pilgrims are extremely limited."

The full article can be found at: (K. Khan, et. al., "Global public health implications of a mass gathering in Mecca, Saudi Arabia during the midst of an influenza pandemic". *Journal of Travel Medicine*, 2010;17(2):75-81). Link not available

[Return to Top](#)

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## **POTENT VESICULAR STOMATITIS VIRUS-BASED AVIAN INFLUENZA VACCINES PROVIDE LONG-TERM STERILIZING IMMUNITY AGAINST HETEROLOGOUS CHALLENGE**

TB & Outbreaks Week

May 11, 2010

"Here we have generated and characterized VSV-based vaccines that express the A/Hong Kong/156/1997 (clade 0) H5 HA from the first position of the VSV genome. These vectors induce broadly cross-neutralizing antibodies against homologous and heterologous H5N1 viruses of different clades in mice. The vaccines provide complete protection against morbidity and mortality after heterologous challenge with clade 0 and clade 1 strains in animals even 1 year after vaccination. Postchallenge pulmonary virus loads show that these vectors provide sterilizing immunity."

"Therefore, VSV-based AIV vaccines are potent, broadly cross-protective pandemic vaccine candidates."

The full article can be found at: (J.A. Schwartz, et. al., "Potent vesicular stomatitis virus-based avian influenza vaccines provide long-term sterilizing immunity against heterologous challenge". *Journal of Virology*, 2010;84(9):4611-8). Link not available.

[Return to Top](#)

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## **PB1-F2 EXPRESSION BY THE 2009 PANDEMIC H1N1 INFLUENZA VIRUS HAS MINIMAL IMPACT ON VIRULENCE IN ANIMAL MODELS**

Life Science Weekly

May 11, 2010

"Unlike previous pandemic viruses, the 2009 H1N1 pandemic influenza virus does not code for the virulence factor PB1-F2. The genome of the 2009 H1N1 virus contains three stop codons preventing PB1-F2 expression; however, PB1-F2 production could occur following genetic mutation or reassortment."

"Thus, it is of great interest to understand the impact that expression of the PB1-F2 protein might have in the context of the 2009 pandemic influenza virus, A/California/04/2009 (Cal/09). We have addressed this question by generating two Cal/09 viruses with productive PB1-F2 open reading frames containing

either an asparagine at position 66 of PB1-F2 (66N) or a serine at position 66 (66S): this N66S change has previously been shown to be associated with increased virulence in mice. We used these viruses to investigate the effect on virulence conferred by expression of the 66N or the 66S PB1-F2 protein in both in vitro and in vivo systems. Our results show enhanced replication of the 66S virus in A549 cells, while studies of BALB/c and DBA/2 mice and ferrets revealed no significant differences in symptoms of infection with wild-type Cal/09 versus the 66N or 66S virus variant. Also, coinfection of mice with *Streptococcus pneumoniae* and the different viruses (recombinant wild-type [rWT] Cal/09 and the 66N and 66S viruses) did not result in significant differences in mortality. Mice infected with either PB1-F2-expressing virus did demonstrate altered protein levels of proinflammatory cytokines; differences were observed to be greater in infection caused by the 66S virus."

"In summary, our study demonstrates that PB1-F2 expression by the Cal/09 virus modulates the immune response to infection while having a minimal effect on virus virulence in two mammalian models."

The full article can be found at: (R. Hai, et. al., "PB1-F2 expression by the 2009 pandemic H1N1 influenza virus has minimal impact on virulence in animal models". *Journal of Virology*, 2010;84(9):4442-50). Link not available.

[Return to Top](#)

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## **ALTERNATIVE LIVE-ATTENUATED INFLUENZA VACCINES BASED ON MODIFICATIONS IN THE POLYMERASE GENES PROTECT AGAINST EPIDEMIC AND PANDEMIC FLU**

Virus Weekly  
May 11, 2010

"We have previously shown that mutations in the PB1 and PB2 genes of the live-attenuated influenza vaccine (LAIV) from the cold-adapted (ca) influenza virus A/Ann Arbor/6/60 (H2N2) could be transferred to avian influenza viruses and produce partially attenuated viruses. We also demonstrated that avian influenza viruses carrying the PB1 and PB2 mutations could be further attenuated by stably introducing a hemagglutinin (HA) epitope tag in the PB1 gene. In this work, we wanted to determine whether these modifications would also result in attenuation of a so-called triple reassortant (TR) swine influenza virus (SIV). Thus, the TR influenza A/swine/Wisconsin/14094/99 (H3N2) virus was generated by reverse genetics and subsequently mutated in the PB1 and PB2 genes. Here we show that a combination of mutations in this TR backbone results in an attenuated virus in vitro and in vivo. Furthermore, we show the potential of our TR backbone as a vaccine that provides protection against the 2009 swine-origin pandemic influenza H1N1 virus (S-OIV) when carrying the surface of a classical swine strain. We propose that the availability of alternative backbones to the conventional ca A/Ann Arbor/6/60 LAIV strain could also be useful in epidemic and pandemic influenza and should be considered for influenza vaccine development."

"In addition, our data provide evidence that the use of these alternative backbones could potentially circumvent the effects of original antigenic sin (OAS) in certain circumstances."

The full article can be found at: (A. Solorzano, et. al., "Alternative live-attenuated influenza vaccines based on modifications in the polymerase genes protect against epidemic and pandemic flu". *Journal of Virology*, 2010;84(9):4587-96). Link not available.

[Return to Top](#)

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## **ANTIGENIC AND GENETIC DIVERSITY OF HIGHLY PATHOGENIC AVIAN INFLUENZA A (H5N1) VIRUSES ISOLATED IN EGYPT**

Medical Letter on the CDC & FDA  
May 16, 2010

"Previous reports identified antigenic similarities between viruses belonging to clack [sic] 2.2. However, poultry and human viruses isolated in northern Egypt during 2007 and 2008 were found to be

antigenically distinct from other clade 2.2 viruses from this country. Genetic analysis of the hemagglutinin revealed a high degree of nucleotide and amino acid divergence."

"The antigenic changes in Egyptian viruses isolated during 2007-08 necessitated that two of these strains be considered as potential H5N1 pre-pandemic vaccine candidates."

The full article can be found at: (A.L. Balish, et. al., "Antigenic and Genetic Diversity of Highly Pathogenic Avian Influenza A (H5N1) Viruses Isolated in Egypt. Avian Diseases", 2010;54(1 Suppl. S):329-334). Link not available.

[Return to Top](#)

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## **DEVELOPMENT AND EVALUATION OF A ONE-STEP REAL-TIME RT-PCR ASSAY FOR UNIVERSAL DETECTION OF INFLUENZA A VIRUSES FROM AVIAN AND MAMMAL SPECIES**

TB & Outbreaks Week

May 18, 2010

"The objective of our study was to develop and evaluate a TaqMan real-time RT-PCR (RRT-PCR) assay for universal detection of influenza A (IA) viruses. The primers and LNA-modified octanucleotide probe were selected to correspond to extremely conserved regions of the membrane protein (MP) segment identified by a comprehensive bioinformatics analysis including 10,405 IA viruses MP sequences, i.e., all of the sequences of the Influenza Virus Sequence database collected as of August 20, 2009."

"The RRT-PCR has a detection limit of approximately five copies of target RNA/reaction and excellent reaction parameters tested in four IA viruses reference laboratories. The inclusivity of the assay was estimated at both the bioinformatic and the experimental level."

"Our results predicted that this RRT-PCR assay was able to detect 99.5% of known human IA virus strains, 99.84% of pandemic influenza A (H1N1) strains, 99.75% of avian strains, 98.89% of swine strains, 98.15% of equine strains, and 100% of influenza A viruses of other origin."

The full article can be found at: (A. Nagy, et. al., "Development and evaluation of a one-step real-time RT-PCR assay for universal detection of influenza A viruses from avian and mammal species". Archives of Virology, 2010;155(5):665-73). Link not available.

[Return to Top](#)

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## **MODELING HOST RESPONSES IN FERRETS DURING A/CALIFORNIA/07/2009 INFLUENZA INFECTION**

Obesity, Fitness & Wellness Week

May 22, 2010

"Using an experimental infection model in ferrets, we examined the pathological features and characterized the host immune responses by using microarray analysis, during infection with 2009-H1N1 A/California/07/2009 and seasonal A/Brisbane/59/2007."

"Chemokines CCL2, CCL8, CXCL7 and CXCL10 along with the majority of interferon-stimulated genes were expressed early, correlated to lung pathology, and abruptly decreased expression on day 7 following infection of A/California/07/2009. Interestingly, the drop in innate immune gene expression was replaced by a significant increase of the adaptive immune genes for granzymes and immunoglobulins. Serum anti-influenza antibodies were first observed on day 7, commensurate with the viral clearance."

"We propose that lung pathology in humans occurs during the innate phase of host immunity and a delay or failure to switch to the adaptive phase may contribute to morbidity and mortality during severe 2009-H1N1 infections."

The full article can be found at: (T. Rowe, et. al., "Modeling host responses in ferrets during A/California/07/2009 influenza infection". *Virology*, 2010;401(2):257-65). Link not available.  
[Return to Top](#)

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