

15 June 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 #116

1. INFLUENZA A VIRAL LOADS IN RESPIRATORY SAMPLES COLLECTED FROM PATIENTS INFECTED WITH PANDEMIC H1N1, SEASONAL H1N1 AND H3N2

VIRUSES: *“Based on M gene copy numbers, we conclude that NPA is the best specimen for detection of influenza A viruses, and followed in order by NS and TS.”*

2. LOW SEROPROTECTION AGAINST PRESEASONAL INFLUENZA LOCAL STRAINS IN CHILDREN MIGHT PREDICT THE UPCOMING EPIDEMIC INFLUENZA STRAINS:

“The dominant winter influenza strains in Taiwan were B/Malaysia/2506/2004•like in the 2006–2007 season, A/Brisbane/59/2007•like virus (H1N1) in the 2007–2008 season, and A/Brisbane/59/2007•like virus (H1N1) in the 2008–2009 season..... The emergence of these viruses correlated well with the circulating influenza subtype in the following winter peak seasons.”

3. SELECTION FOR RESISTANCE TO OSELTAMIVIR IN SEASONAL AND PANDEMIC H1N1 INFLUENZA AND WIDESPREAD CO-CIRCULATION OF THE LINEAGES:

“By combining phylogenetic and geographic data we have thus far identified 53 areas of co-circulation where reassortment can occur. At our website POINTMAP, <http://pointmap.osu.edu> we make available a visualization and an application for updating these results as more data are released.

4. DEATHS FROM SEASONAL INFLUENZA AMONG PREGNANT WOMEN IN THE UNITED STATES, 1998-2005:

“On average, five possible influenza-related deaths among pregnant women were reported per year before the emergence of pregnancy-related deaths due to the current H1N1 pandemic compared with the 28 laboratory-confirmed, pregnancy-related deaths reported for the first 4 months of the 2009 pandemic.”

5. IN VITRO ANTIVIRAL ACTIVITY OF FAVIPIRAVIR (T-705) AGAINST DRUG-RESISTANT INFLUENZA AND 2009 A(H1N1) VIRUSES:

“This study demonstrates that favipiravir inhibits in vitro replication of a wide range of influenza viruses, including those resistant to currently available drugs.”

6. COMPARISON OF EGG AND HIGH YIELDING MDCK CELL-DERIVED LIVE

ATTENUATED INFLUENZA VIRUS FOR COMMERCIAL PRODUCTION OF TRIVALENT INFLUENZA VACCINE: IN VITRO CELL SUSCEPTIBILITY AND INFLUENZA VIRUS REPLICATION KINETICS IN PERMISSIVE AND SEMI-PERMISSIVE CELLS: *“Based on these study results we conclude that the MDCK cell produced and egg produced vaccine strains are highly comparable.”*

CB Daily Report

Chem-Bio News

INFLUENZA A VIRAL LOADS IN RESPIRATORY SAMPLES COLLECTED FROM PATIENTS INFECTED WITH PANDEMIC H1N1, SEASONAL H1N1 AND H3N2 VIRUSES

Genomics & Genetics Weekly
June 18, 2010

“In this study, quantitative real time RT-PCR specific for M gene was used to determine influenza A viral loads present in NS, NPA and TS samples collected from patients infected with the 2009 pandemic H1N1, seasonal H1N1 and H3N2 viruses. Various copy numbers of RNA transcripts derived from recombinant plasmids containing complete M gene insert of each virus strain were assayed by RT-PCR. A standard curve for viral RNA quantification was constructed by plotting each Ct value against the log quantity of each standard RNA copy number. Copy numbers of M gene were obtained through the extrapolation of Ct values of the test samples against the corresponding standard curve. Among a total of 29 patients with severe influenza enrolled in this study (12 cases of the 2009 pandemic influenza, 5 cases of seasonal H1N1 and 12 cases of seasonal H3N2 virus), NPA was found to contain significantly highest amount of viral loads and followed in order by NS and TS specimen. Viral loads among patients infected with those viruses were comparable regarding type of specimen analyzed.”

The full article can be found at: (N. Ngaosuwankul, et. al., “Influenza A viral loads in respiratory samples collected from patients infected with pandemic H1N1, seasonal H1N1 and H3N2 viruses”. Virology Journal, 2010;7():75). Link not available.

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LOW SEROPROTECTION AGAINST PRESEASONAL INFLUENZA LOCAL STRAINS IN CHILDREN MIGHT PREDICT THE UPCOMING EPIDEMIC INFLUENZA STRAINS

By Wei•Ju Su, Pei•Lan Shao, Ming•Tsan Liu, Ding•Ping Liu, Kuo•Chin Huang, Luan•Yin Chang, Chun•Yi Lu, Jen•Ren Wang, Shin•Ru Shih, Daniel Tsung•Ning Huang, Hsin Chi, and Li•Min Huang
Clinical Infectious Diseases
June 08, 2010

“Background. Our objective was to determine the serological signals that indicated the

possible dominant circulating influenza virus subtypes for the coming influenza seasons.

Methods. Healthy children 6 months through 5 years of age, adults 18–60 years of age, and elderly adults >60 years of age were recruited to receive seasonal trivalent inactivated influenza vaccinations from October through December during the 2006–2007 and 2008–2009 seasons. Paired serum samples were collected at baseline and at 3 weeks after vaccination. Using a hemagglutination inhibition (HAI) assay, we measured antibody responses to local influenza strains circulating early in October, before each winter influenza season.

Results. A total of 301 subjects were tested for antibody to local strains (80, 120, and 101 subjects in the 2006–2007, 2007–2008, and 2008–2009 seasons, respectively). The dominant winter influenza strains in Taiwan were B/Malaysia/2506/2004•like in the 2006–2007 season, A/Brisbane/59/2007•like virus (H1N1) in the 2007–2008 season, and A/Brisbane/59/2007•like virus (H1N1) in the 2008–2009 season. The group with the lowest number of subjects with an HAI titer of 40 at baseline was children with antibody against the B/Taiwan/0050/2006 in the 2006–2007 season, A/Taiwan/785/2006 (H1N1) in 2007–2008 season, and A/Taiwan/951/2007 (H1N1) in 2008–2009 season. The emergence of these viruses correlated well with the circulating influenza subtype in the following winter peak seasons.

Conclusions. Low seroprotection rate among children against a specific locally circulating influenza strain might predict the dominantly circulating subtype of influenza virus in the coming winter season. A year•end preseasonal serological survey of children could provide valuable information about the possible circulating strain and tailor the disease•control strategy accordingly.”

The full article can be found at: <http://www.journals.uchicago.edu/doi/abs/10.1086/653532>

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SELECTION FOR RESISTANCE TO OSELTAMIVIR IN SEASONAL AND PANDEMIC H1N1 INFLUENZA AND WIDESPREAD CO-CIRCULATION OF THE LINEAGES

Medical Letter on the CDC & FDA

June 13, 2010

“There are currently two main branches of H1N1 circulating in humans, a seasonal branch and a pandemic branch. The primary treatment method for pandemic and seasonal H1N1 is the antiviral drug Tamiflu (oseltamivir). Although many seasonal H1N1 strains around the world are resistant to oseltamivir, initially, pandemic H1N1 strains have been susceptible to oseltamivir. As of February 3, 2010, there have been reports of resistance to oseltamivir in 225 cases of H1N1 pandemic influenza. The evolution of resistance to oseltamivir in pandemic H1N1 could be due to point mutations in the neuraminidase or a reassortment event between seasonal H1N1 and pandemic H1N1 viruses that provide a neuraminidase carrying an oseltamivir-resistant genotype to pandemic H1N1. Using phylogenetic analysis of

neuraminidase sequences, we show that both seasonal and pandemic lineages of H1N1 are evolving to direct selective pressure for resistance to oseltamivir. Moreover, seasonal lineages of H1N1 that are resistant to oseltamivir co-circulate with pandemic H1N1 throughout the globe. By combining phylogenetic and geographic data we have thus far identified 53 areas of co-circulation where reassortment can occur. At our website POINTMAP, <http://pointmap.osu.edu> we make available a visualization and an application for updating these results as more data are released. As oseltamivir is a keystone of preparedness and treatment for pandemic H1N1, the potential for resistance to oseltamivir is an ongoing concern."

The full article can be found at: (D.A. Janies, et. al., "Selection for resistance to oseltamivir in seasonal and pandemic H1N1 influenza and widespread co-circulation of the lineages". International Journal of Health Geographics, 2010;9():13). Link not available.

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DEATHS FROM SEASONAL INFLUENZA AMONG PREGNANT WOMEN IN THE UNITED STATES, 1998-2005

Life Science Weekly
June 15, 2010

"Centers for Disease Control and Prevention's (CDC) Pregnancy Mortality Surveillance System (PMSS) database for the years 1998-2005. PMSS collects de-identified copies of vital records supplied by all 50 states, the District of Columbia, and New York City for women who died during or within 1 year after pregnancy. Records in the database broadly classified under deaths due to respiratory infections were identified, and the corresponding archived death certificates were individually reviewed to classify the cause of death as pneumonia or influenza. Between 1998 and 2005, 4,693 pregnancy-related deaths were reported to CDC. Of these, 78 women died from influenza or pneumonia; 40 of these deaths occurred during an influenza season. Nearly 75% of deaths occurred during or within 2 weeks of the end of the pregnancy. On average, five possible influenza-related deaths among pregnant women were reported per year before the emergence of pregnancy-related deaths due to the current H1N1 pandemic compared with the 28 laboratory-confirmed, pregnancy-related deaths reported for the first 4 months of the 2009 pandemic."

"This highlights the excess mortality among pregnant women resulting from this pandemic influenza virus."

The full article can be found at: (W.M. Callaghan, et. al., "Deaths From Seasonal Influenza Among Pregnant Women in the United States, 1998-2005". Obstetrics and Gynecology, 2010;115(5):919-923). Link not available.

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IN VITRO ANTIVIRAL ACTIVITY OF FAVIPIRAVIR (T-705) AGAINST DRUG-

RESISTANT INFLUENZA AND 2009 A(H1N1) VIRUSES

Biotech Week

June 9, 2010

"Favipiravir (T-705) has previously been shown to have a potent antiviral effect against influenza virus and some other RNA viruses in both cell culture and in animal models. Currently, favipiravir is undergoing clinical evaluation for the treatment of influenza A and B virus infections."

"In this study, favipiravir was evaluated in vitro for its ability to inhibit the replication of a representative panel of seasonal influenza viruses, the 2009 A(H1N1) strains, and animal viruses with pandemic (pdm) potential (swine triple reassortants, H2N2, H4N2, avian H7N2, and avian H5N1), including viruses which are resistant to the currently licensed anti-influenza drugs. All viruses were tested in a plaque reduction assay with MDCK cells, and a subset was also tested in both yield reduction and focus inhibition (FI) assays. For the majority of viruses tested, favipiravir significantly inhibited plaque formation at 3.2 mcM (0.5 microg/ml) (50% effective concentrations [EC(50).] of 0.19 to 22.48 mcM and 0.03 to 3.53 microg/ml), and for all viruses, with the exception of a single dually resistant 2009 A (H1N1) virus, complete inhibition of plaque formation was seen at 3.2 mcM (0.5 microg/ml). Due to the 2009 pandemic and increased drug resistance in circulating seasonal influenza viruses, there is an urgent need for new drugs which target influenza."

"This study demonstrates that favipiravir inhibits in vitro replication of a wide range of influenza viruses, including those resistant to currently available drugs."

The full article can be found at: (K. Sleeman, et. al., "In Vitro antiviral activity of favipiravir (T-705) against drug-resistant influenza and 2009 A(H1N1) viruses". Antimicrobial Agents and Chemotherapy, 2010;54(6):2517-24). Link not available.

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COMPARISON OF EGG AND HIGH YIELDING MDCK CELL-DERIVED LIVE ATTENUATED INFLUENZA VIRUS FOR COMMERCIAL PRODUCTION OF TRIVALENT INFLUENZA VACCINE: IN VITRO CELL SUSCEPTIBILITY AND INFLUENZA VIRUS REPLICATION KINETICS IN PERMISSIVE AND SEMI-PERMISSIVE CELLS

Life Science Weekly

June 15, 2010

"Currently MedImmune manufactures cold-adapted (ca) live, attenuated influenza vaccine (LAIV) from specific-pathogen free (SPF) chicken eggs. Difficulties in production scale-up and potential exposure of chicken flocks to avian influenza viruses especially in the event of a pandemic influenza outbreak have prompted evaluation and development of alternative non-egg based influenza vaccine manufacturing technologies."

"As part of MedImmune's effort to develop the live attenuated influenza vaccine (LAIV) using cell culture production technologies we have investigated the use of high yielding, cloned MDCK cells as a substrate for vaccine production by assessing host range and virus

replication of influenza virus produced from both SPF egg and MDCK cell production technologies. In addition to cloned MDCK cells the indicator cell lines used to evaluate the impact of producing LAIV in cells on host range and replication included two human cell lines: human lung carcinoma (A549) cells and human muco-epidermoid bronchiolar carcinoma (NCI H292) cells. The influenza viruses used to infect the indicators cell lines represented both the egg and cell culture manufacturing processes and included virus strains that composed the 2006-2007 influenza seasonal trivalent vaccine (A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/05 (H3N2) and B/Malaysia/2506/04). Results from this study demonstrate remarkable similarity between influenza viruses representing the current commercial egg produced and developmental MDCK cell produced vaccine production platforms. MedImmune's high yielding cloned MDCK cells used for the cell culture based vaccine production were highly permissive to both egg and cell produced ca attenuated influenza viruses. Both the A549 and NCI H292 cells regardless of production system were less permissive to influenza A and B viruses than the MDCK cells. Irrespective of the indicator cell line used the replication properties were similar between egg and the cell produced influenza viruses."

Based on these study results we conclude that the MDCK cell produced and egg produced vaccine strains are highly comparable."

The full article can be found at: (A.I. Hussain, et. al., "Comparison of egg and high yielding MDCK cell-derived live attenuated influenza virus for commercial production of trivalent influenza vaccine: in vitro cell susceptibility and influenza virus replication kinetics in permissive and semi-permissive cells". *Vaccine*, 2010; 28(22): 3848-55). Link not available.

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Steve Tesko: Steve.Tesko@anser.org

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