

16 March 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 #103

1. DETECTION OF NOVEL SWINE ORIGIN INFLUENZA A VIRUS (H1N1) BY REAL-TIME NUCLEIC ACID SEQUENCE-BASED AMPLIFICATION: "Compared with reference methods (viral culture, conventional RT-PCR, and real-time RT-PCR), the sensitivity, specificity, positive predictive value, and negative predictive value of the present assay were all 100%."

2. BROAD-SPECTRUM ANTIVIRAL EFFECT OF AGRIMONIA PILOSA EXTRACT ON INFLUENZA VIRUSES: "The broad-spectrum antiviral activity of Agrimonia pilosa extract on various subtypes of influenza viruses merits further investigation as it may provide a means of managing avian influenza infections in poultry farms and potential avian-human transmission."

3. THE IFITM PROTEINS MEDIATE CELLULAR RESISTANCE TO INFLUENZA A H1N1 VIRUS, WEST NILE VIRUS, AND DENGUE VIRUS: "Collectively this work identifies a family of antiviral restriction factors that mediate cellular innate immunity to at least three major human pathogens."

4. MONOCLONAL ANTIBODIES SPECIFIC FOR DISCONTINUOUS EPITOPES DIRECT REFOLDING OF INFLUENZA A VIRUS HEMAGGLUTININ: "Further, they demonstrate that Abs can facilitate the refolding of denatured proteins, which suggests a number of practical applications for optimizing antibody based assays, and also for potentially using Abs as specific chaperones for protein refolding."

5. ROLE OF ALVEOLAR EPITHELIAL EARLY GROWTH RESPONSE-1 (EGR-1) IN CD8(+) T CELL-MEDIATED LUNG INJURY: "That Egr-1 may represent an important target in mitigating the immunopathology of severe influenza infection."

6. LIKELY SCENARIOS FOR INFLUENZA IN 2010 AND THE 2010/2011 INFLUENZA SEASON IN EUROPE AND THE CONSEQUENT WORK PRIORITIES: "On the basis of this it seems unlikely that there will be another spring/summer pandemic wave in Europe unless there are significant unrecognised uninfected populations or the virus changes and becomes more transmissible."

7. CHARACTERIZING THE INITIAL DIFFUSION PATTERN OF PANDEMIC (H1N1) 2009 USING SURVEILLANCE DATA: "Beginning from 6 initial foci, the spatial distribution has remained heterogeneous at the end of the first three months, with students functioning as the main disseminators."

8. HHS PREPARING TO HANDLE CLAIMS OF HARM FROM H1N1 VACCINE: "As of yesterday [11 March 2010], HHS had received letters from 106 people saying they plan to submit claims for compensation benefits because of problems related to the vaccine, according to David Bowman, a spokesman for HHS's Health Resources and Services Administration (HRSA)."

9. WHO PANDEMIC (H1N1) 2009 - UPDATE 91: "The most active areas of pandemic influenza transmission are currently in Southeast Asia, however, lower levels of pandemic virus circulation persist in other parts of Asia and in Eastern and South-eastern Europe. In West Africa, limited data suggests that pandemic influenza virus transmission may be increasing in region. Of note, seasonal influenza B viruses have been increasingly detected in Asia and appear to be spreading westward."

CB Daily Report

Chem-Bio News

DETECTION OF NOVEL SWINE ORIGIN INFLUENZA A VIRUS (H1N1) BY REAL-TIME NUCLEIC ACID SEQUENCE-BASED AMPLIFICATION

Preventive Medicine Week
February 28, 2010

“In this study, a haemagglutinin (HA) gene-based real-time nucleic acid sequence-based amplification (NASBA) assay was developed for the specific detection of S-OIV (H1N1).”

“The assay was evaluated and validated by comparing it with existing detection methods for S-OIV (H1N1). Results obtained in a 10-fold dilution series assay demonstrated the analytic sensitivity of the present assay was comparable to that of a commercial S-OIV (H1N1) real-time RT-PCR kit and higher than that of the Centers for Disease Control and Prevention (CDC) TaqMan assay. The actual detection limit of the real-time NASBA assay was approximately 50 copies per reaction. Compared with reference methods (viral culture, conventional RT-PCR, and real-time RT-PCR), the sensitivity, specificity, positive predictive value, and negative predictive value of the present assay were all 100%.”

The full article can be found at: (Y. Ge, et. al., “Detection of novel swine origin influenza A virus (H1N1) by real-time nucleic acid sequence-based amplification”. *Journal of Virological Methods*, 2010;163(2):495-7). Link not available.

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BROAD-SPECTRUM ANTIVIRAL EFFECT OF AGRIMONIA PILOSA EXTRACT ON INFLUENZA VIRUSES

Pharma Investments, Ventures & Law Weekly
February 28, 2010

“Here we tested various Korean medicinal plant extracts for potential antiviral activity against influenza viruses.”

“Among them, an extract of *Agrimonia pilosa* was shown to be highly effective against all three subtypes of human influenza viruses including H1N1 and H3N2 influenza A subtypes and influenza B virus. The EC50 value against influenza A virus, as tested by the plaque reduction assay on MDCK cells, was 14-23 μ g/ml. The extract also exhibited a virucidal effect at a concentration of 160-570 ng/ml against influenza A and B viruses when the viruses were treated with the extract prior to plaque assay. In addition, when tested in embryonated chicken eggs the extract exhibited a strong inhibitory effect in ovo on the H9N2 avian influenza virus at a concentration of 280 ng/ml. Quantitative RT-PCR analysis data showed that the extract, to some degree, suppressed viral RNA synthesis in MDCK cells. HI and inhibition of neuraminidase were observed only at high concentrations of the extract. And yet, the extract's antiviral activity required direct contact between it and the virus, suggesting that its antiviral action is mediated by the viral membrane, but does not involve the two major surface antigens, HA and NA, of the virus.”

“The broad-spectrum antiviral activity of *Agrimonia pilosa* extract on various subtypes of influenza viruses merits further investigation as it may provide a means of managing avian influenza infections in poultry farms and potential avian-human transmission.”

The full article can be found at: (W.J. Shin, et. al., “Broad-spectrum antiviral effect of *Agrimonia pilosa* extract on influenza viruses”. *Microbiology and Immunology*, 2010;54(1):11-19). Link not available.

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THE IFITM PROTEINS MEDIATE CELLULAR RESISTANCE TO INFLUENZA A H1N1 VIRUS, WEST NILE VIRUS, AND DENGUE VIRUS

Hospital Business Week
February 28, 2010

“To find host cell modifiers of influenza A H1N1 viral infection, we used a functional genomic screen and

identified over 120 influenza A virus-dependency factors with roles in endosomal acidification, vesicular trafficking, mitochondrial metabolism, and RNA splicing. We discovered that the interferon-inducible transmembrane proteins IFITM1, 2, and 3 restrict an early step in influenza A viral replication. The IFITM proteins confer basal resistance to influenza A virus but are also inducible by interferons type I and II and are critical for interferon's virustatic actions. Further characterization revealed that the IFITM proteins inhibit the early replication of flaviviruses, including dengue virus and West Nile virus."

"Collectively this work identifies a family of antiviral restriction factors that mediate cellular innate immunity to at least three major human pathogens."

The full article can be found at: (A.L. Brass, et. al., "The IFITM Proteins Mediate Cellular Resistance to Influenza A H1N1 Virus, West Nile Virus, and Dengue Virus". Cell, 2009;139(7):1243-1254). Link not available.

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MONOCLONAL ANTIBODIES SPECIFIC FOR DISCONTINUOUS EPITOPES DIRECT REFOLDING OF INFLUENZA A VIRUS HEMAGGLUTININ

Pharma Investments, Ventures & Law Weekly
February 28, 2010

"Antibodies (Abs) specific for the globular domain of influenza A virus hemagglutinin (HA) efficiently neutralize viral infectivity and provide the most effective protection against influenza following infection or vaccination. Nearly all neutralizing Abs recognize discontinuous determinants formed by residues present on different stretches of the HA primary structure."

"Here, I show that approximately 25% of a large panel of neutralizing monoclonal Abs (mAbs), including Abs specific for each of the four major antigenic sites, can bind to completely denatured HA. Binding of these mAbs to denatured HA occurs much more slowly than binding to native HA, but bound mAbs dissociate from denatured and native HA with similar kinetics, and amino acid substitutions that reduce mAb binding to native HA have a similar effect on mAb interaction with denatured HA. HA refolding induced by mAb binding facilitated the binding of mAbs to other antigenic sites, indicating that refolding was not limited to the antibody-interaction domain. These findings validate the localization of antigenic sites by identifying amino acid substitutions selected in mAb escape mutants."

"Further, they demonstrate that Abs can facilitate the refolding of denatured proteins, which suggests a number of practical applications for optimizing antibody based assays, and also for potentially using Abs as specific chaperones for protein refolding."

The full article can be found at: (.W Yewdell, et. al., "Monoclonal antibodies specific for discontinuous epitopes direct refolding of influenza A virus hemagglutinin". Molecular Immunology, 2010;47(5):1132-6). Link not found.

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ROLE OF ALVEOLAR EPITHELIAL EARLY GROWTH RESPONSE-1 (EGR-1) IN CD8(+) T CELL-MEDIATED LUNG INJURY

Pharma Investments, Ventures & Law Weekly
February 28, 2010

"We have used a mouse model to specifically investigate the role of antiviral CD8(+) T cells in this injury, and have found that the critical effector molecule is TNF-alpha expressed by the T cells upon antigen recognition."

"Interestingly, the immunopathology which ensues is characterized by significant accumulation of host inflammatory cells, recruited by chemokines expressed by the target alveolar epithelial cells. In this study we analyzed the mechanisms involved in the induction of epithelial chemokine expression triggered by antigen-specific CD8(+) T cell recognition, and demonstrate that the early growth

response-1 (Egr-1) transcription factor is rapidly induced in epithelial cells, both in vitro and ex vivo, and that this is a critical regulator of a host of inflammatory chemokines. Genetic deficiency of Egr-1 significantly abrogates both the chemokine expression and the immunopathologic injury associated with T cell recognition, and it directly regulates transcriptional activity of a model CXC chemokine, MIP-2. We further demonstrate that Egr-1 induction is triggered by TMF-alpha-dependant ERK activation, and inhibition of this pathway ablates Egr-1 expression."

"That Egr-1 may represent an important target in mitigating the immunopathology of severe influenza infection."

The full article can be found at: (C.V. Ramana, et. al., "Role of alveolar epithelial early growth response-1 (Egr-1) in CD8(+) T cell-mediated lung injury". Molecular Immunology, 2009;47(2-3):623-631). Link not available.

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LIKELY SCENARIOS FOR INFLUENZA IN 2010 AND THE 2010/2011 INFLUENZA SEASON IN EUROPE AND THE CONSEQUENT WORK PRIORITIES

European Centre for Disease Prevention and Control
March 2010

"On the basis of this it seems unlikely that there will be another spring/summer pandemic wave in Europe unless there are significant unrecognised uninfected populations or the virus changes and becomes more transmissible. Serological surveys (measuring the levels of immunity in the community) could help reduce this uncertainty. However, only a limited number of Member States are currently using this tool to assess susceptibility. Other important data and analyses are lacking and hence priority work has been identified for Member States and ECDC to undertake, especially to inform vaccination strategies using the currently authorised monovalent pandemic vaccines and the anticipated 2010/2011 seasonal trivalent influenza vaccines (which will include the pandemic H1N1 strain).

It seems highly likely that even when WHO judges the post-peak and post-pandemic phases to have been reached, Europe will continue to experience low-level transmission and small outbreaks of the pandemic 2009 A(H1N1) influenza. This is the most likely scenario throughout the whole of 2010. However, larger outbreaks cannot be excluded given the lack of information from seroepidemiology.

Epidemic transmission of the pandemic virus is highly likely in the next (2010/2011) winter season, at least in very young children and other susceptible individuals. It is also most likely that pandemic influenza A(H1N1) will become the dominant virus in the coming winter season along with influenza B viruses, though the presence of influenza A(H3N2) viruses as well cannot presently be excluded. By then Europe will probably be referring to this combination as the 'new seasonal influenza'.

There is currently no evidence of a changed pathogenicity of the circulating pandemic influenza virus. No significant genetic or antigenic changes to the pandemic influenza virus have so far been reported and so patterns in morbidity and mortality similar to those seen during the pandemic should initially be expected from this virus next winter though numbers of cases will be considerably smaller because of the previous transmission and vaccination.

In summary, the implications for vaccination strategies from this conservative forward look is that transmission of the pandemic virus will continue through 2010 albeit at low levels, and that this will be the predominant influenza A virus causing seasonal influenza in the winter of 2010/2011. At present the currently authorised monovalent pandemic vaccines and the new 2010/2011 seasonal influenza vaccines are likely to be effective against the 2009 A(H1N1) strain for the coming 6-10 months. Therefore, for Member States wishing to protect unimmunised citizens in the spring of 2010 and autumn/winter of 2010-2011, there will be advantages to continuing to offer these vaccines (or trivalent vaccines with the pandemic antigen when they are available) to their chosen risk and target groups. ECDC's advice to EU citizens remains to accept influenza vaccination when it is offered to them."

The full article can be found at:

http://www.ecdc.europa.eu/en/healthtopics/H1N1/Documents/1003_RA_forward_look_influenza.pdf

CHARACTERIZING THE INITIAL DIFFUSION PATTERN OF PANDEMIC (H1N1) 2009 USING SURVEILLANCE DATA

By Shui Shan Lee and Ngai Sze Wong

PloS Currents - Influenza

March 13, 2010

“Using notification data, diffusion of pandemic human influenza A (H1N1) 2009 in Hong Kong was explored with geographic information system (GIS) methodology. Point data were displayed and then analysed with interpolation and the application of SaTScan™. Beginning from 6 initial foci, the spatial distribution has remained heterogeneous at the end of the first three months, with students functioning as the main disseminators. Our study showed that routinely collected surveillance data could be effectively used for describing the epidemic, which could support the development of interventions at local levels.”

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“Our study showed that swine flu has not been spreading swiftly across the territory in the initial phase since the first case was discovered. At the end of the first three month period, one fifth of the DCCAs, each with a similar population size, have reported no more than 5 cases. A combination of SaTScan™ and IDW methodologies has enabled us to highlight six initial foci with spatial diffusion on Hong Kong Island and Kowloon Peninsula, the highly urbanized regions in Hong Kong. There were smaller temporo-spatial clusters of infections beyond these densely populated areas. The relatively “slow” pace of spread supports the observations reported by other researchers that airborne transmission of swine flu was lacking.[12] The virus has presumably permeated through the population via close person-to-person contacts. The mapping of residence locations of all reported cases is therefore a valid investigative approach. Interactions within households and with neighbours in close spatial proximity should have underlain swine flu diffusion in the population. The slow diffusing pattern is in line with the relatively low basic reproductive number of 1 to 3, [13][14][15] compared to that of measles, an airborne virus. Interestingly, household transmission, though important, may in fact be less efficient than seasonal influenza,[16][17] though this remains to be confirmed. By separating the geocoded cases into students and non-students, we further determined that student infections tended to be more clustered. If all student cases were excluded, the connectivity among swine flu cases in the community became very loose and might not have led to the subsequent epidemic. Students were therefore likely to be the main virus disseminators across Hong Kong, as has been reported in other countries for swine flu.[18][19] and seasonal influenza.[20]”

The full article can be found at: <http://knol.google.com/k/shui-shan-lee/characterizing-the-initial-diffusion/3cf0o6sqtq33/2?collectionId=28qm4w0q65e4w.1&position=1>

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HHS PREPARING TO HANDLE CLAIMS OF HARM FROM H1N1 VACCINE

By Robert Roos

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

March 12, 2010

“As of yesterday, HHS had received letters from 106 people saying they plan to submit claims for compensation benefits because of problems related to the vaccine, according to David Bowman, a spokesman for HHS's Health Resources and Services Administration (HRSA).

At this point HRSA is accepting only letters of intent to file claims, rather than actual claims, because the administrative policies and procedures for handling them have not yet been approved, Bowman reported. He said the agency has no information yet on what kinds of injuries people are claiming.

People who believe they were injured by the H1N1 vaccine, or by certain other pandemic-related

medical items such as flu antiviral drugs, must write to HHS about it within a year from when they were vaccinated or treated, according to the agency. That preserves their right to file a claim later, after the regulations for claim processing have been approved.”

The full article can be found at:

<http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/mar1210comp.html>

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WHO PANDEMIC (H1N1) 2009 - UPDATE 91

World Health Organization

March 12, 2010

“As of 7 March 2010, worldwide more than 213 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 16713 deaths.

WHO is actively monitoring the progress of the pandemic through frequent consultations with the WHO Regional Offices and member states and through monitoring of multiple sources of information.”

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“The most active areas of pandemic influenza transmission are currently in Southeast Asia, however, lower levels of pandemic virus circulation persist in other parts of Asia and in Eastern and South-eastern Europe. In West Africa, limited data suggests that pandemic influenza virus transmission may be increasing in region. Of note, seasonal influenza B viruses have been increasingly detected in Asia and appear to be spreading westward.”

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“Although pandemic influenza virus continues to be the predominant circulating influenza virus worldwide, circulation of seasonal influenza B viruses continue to increase and spread across Asia, parts of Eastern Europe, and Eastern Africa, but most notably in China, Mongolia, Iran and the Russian Federation.”

The full article can be found at: http://www.who.int/csr/don/2010_03_12/en/index.html

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