27 October 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 #84

1. MIXED INFECTION AND THE GENESIS OF INFLUENZA VIRUS DIVERSITY: *"These results reveal that individuals can harbor influenza viruses that differ in major phenotypic properties, including those that are antigenically distinct and those that differ in their sensitivity to antiviral agents."*

2. NUCLEOSIDE MONOPHOSPHATE COMPLEX STRUCTURES OF THE ENDONUCLEASE DOMAIN FROM THE INFLUENZA VIRUS POLYMERASE PA SUBUNIT REVEAL THE SUBSTRATE BINDING SITE INSIDE THE CATALYTIC CENTER: *"The identification of this binding pocket opens a new avenue for anti-influenza drug discovery, targeting the cap-dependent endonuclease, in response to the worldwide threat of influenza."*

3. CALL FOR EARLY HOSPITAL DISCHARGE TO AVOID SWINE FLU MRSA RISK: *"A rise in hospital infections may accompany a second wave of swine flu, according to the MRSA Working Group."*

4. VIRAL GENETIC DETERMINANTS OF H5N1 INFLUENZA VIRUSES THAT CONTRIBUTE TO CYTOKINE DYSREGULATION: *"Our results suggest that the H5N1 polymerase gene segments, and to a lesser extent the NS gene segment, contribute to cytokine hyperinduction in human macrophages and that a putative H5 pandemic virus that may arise through genetic reassortment between H5N1 and one of the current seasonal influenza viruses may have a markedly altered cytokine phenotype."*

5. T-CELL TOLERANCE FOR VARIABILITY IN AN HLA CLASS I-PRESENTED INFLUENZA A VIRUS EPITOPE: *"These data demonstrate that substitutions at P4 and/or P6 facilitate influenza virus escape from T-cell recognition and provide a model for the number, nature, and location of viral mutations that influence T-cell cross-recognition."*

6. EVALUATION OF AN EPITOPE-BLOCKING ENZYME-LINKED IMMUNOSORBENT ASSAY FOR THE DETECTION OF ANTIBODIES TO INFLUENZA A VIRUS IN DOMESTIC AND WILD AVIAN AND MAMMALIAN SPECIES: *"Evaluation of an epitope-blocking enzyme-linked immunosorbent assay for the detection of antibodies to influenza A virus in domestic and wild avian and mammalian species."*

7. TARGETED VS. SYSTEMATIC EARLY ANTIVIRAL TREATMENT AGAINST A(H1N1)V INFLUENZA WITH NEURAMINIDASE INHIBITORS IN PATIENTS WITH INFLUENZA-LIKE SYMPTOMS: CLINICAL AND ECONOMIC IMPACT: *"Patients who present to care with ILI during an A(H1N1)v influenza epidemic wave should initiate treatment with neuraminidase inhibitors, regardless of risk status. Administering neuraminidase inhibitors between epidemic waves, when the probability of influenza is low, is less effective and cost-effective."*

8. FDA AUTHORIZES EMERGENCY USE OF INTRAVENOUS ANTIVIRAL PERAMIVIR FOR 2009 H1N1 INFLUENZA FOR CERTAIN PATIENTS, SETTINGS: *"Specifically, IV peramivir is authorized only for hospitalized adult and pediatric patients for whom therapy with an IV drug is clinically appropriate, based on one or more of the following reasons….."*

9. INFLUENZA PANDEMIC (H1N1) 2009 (76): EL SALVADOR, DENGUE CO-INFECTION: *"In the eastern zone of the country, there have been reports of patients with simultaneous infection [co-infection] of influenza A (H1N1) and classical dengue fever, confirmed by the Vice Minister of Health, Eduardo Espinoza. In total, there have been 4 such cases of co-infection in the country nationwide."*

CB Daily Report

Chem-Bio News

MIXED INFECTION AND THE GENESIS OF INFLUENZA VIRUS DIVERSITY
Biotech Week
October 21, 2009

"This would require that viruses of both subtypes coinfect the same cells, generating a mixed infection, and then reassort. Determining the nature and frequency of mixed infection with influenza virus is therefore central to understanding the emergence of pandemic, antigenic, and drug-resistant strains. To better understand the potential for such events, we explored patterns of intrahost genetic diversity in recently circulating strains of human influenza virus. By analyzing multiple viral genome sequences sampled from individual influenza patients we reveal a high level of mixed infection, including diverse lineages of the same influenza virus subtype, drug-resistant and-sensitive strains, those that are likely to differ in antigenicity, and even viruses of different influenza virus types (A and B)."

"These results reveal that individuals can harbor influenza viruses that differ in major phenotypic properties, including those that are antigenically distinct and those that differ in their sensitivity to antiviral agents."

The full article can be found at: (E. Ghedin, et. al., "Mixed Infection and the Genesis of Influenza Virus Diversity". Journal of Virology, 2009;83(17):8832-8841). Link not available.
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NUCLEOSIDE MONOPHOSPHATE COMPLEX STRUCTURES OF THE ENDONUCLEASE DOMAIN FROM THE INFLUENZA VIRUS POLYMERASE PA SUBUNIT REVEAL THE SUBSTRATE BINDING SITE INSIDE THE CATALYTIC CENTER
Drug Week
October 23, 2009

"Following the reported crystal structure of the endonuclease domain from the avian influenza virus polymerase PA subunit, here we report the results of a systematic X-ray crystallographic analysis of its complex with adenosine, uridine, and thymidine nucleoside monophosphates (NMPs)."

"Electron density corresponding to the monophosphate moiety of each nucleotide was apparent in each NMP complex and bound to the catalytic metal. A hydrophobic site was found to contribute to nucleoside binding. The NMP complex structures should represent the conformation of the bound product after nuclease cleavage. Moreover, one solvent molecule was found to occupy an equivalent position to the second reported Mn2+ ion, where it mediates the interaction between bound NMPs and the N-terminal PA domain in the presence of the Mg2+ ion. The results presented here indicate a possible cleavage mechanism and identify a distinct nucleotide binding pocket."

"The identification of this binding pocket opens a new avenue for anti-influenza drug discovery, targeting the cap-dependent endonuclease, in response to the worldwide threat of influenza."

The full article can be found at: (C. Zhao, et. al., "Nucleoside Monophosphate Complex Structures of the Endonuclease Domain from the Influenza Virus Polymerase PA Subunit Reveal the Substrate Binding Site inside the Catalytic Center". Journal of Virology, 2009;83(18):9024-9030). Link not available.
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CALL FOR EARLY HOSPITAL DISCHARGE TO AVOID SWINE FLU MRSA RISK
NursingTimes.net

October 20, 2009

"A rise in hospital infections may accompany a second wave of swine flu, according to the MRSA Working Group."

.....

"It warns that a swine-flu pandemic would see a rise in hospital admission and bed occupancy rates, thus leading to conditions under which superbug infections would flourish."

The full article can be found at: http://www.nursingtimes.net/whats-new-in-nursing/specialists/infection-control/call-for-early-hospital-discharge-to-avoid-swine-flu-mrsa-risk/5007563.article?referrer=RSS
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VIRAL GENETIC DETERMINANTS OF H5N1 INFLUENZA VIRUSES THAT CONTRIBUTE TO CYTOKINE DYSREGULATION
Biotech Law Weekly
October 23, 2009

"In comparison with human seasonal influenza (H1N1) viruses, clade 1, 2.1, and 2.2 H5N1 viruses induced higher levels of tumor necrosis factor-alpha in primary human macrophages. To understand viral genetic determinants responsible for this hyperinduction of cytokines, we constructed recombinant viruses containing different combinations of genes from high-cytokine (A/Vietnam/1203/04) and low-cytokine (A/WSN/33) phenotype H1N1 viruses and tested their cytokine-inducing phenotype in human macrophages."

"Our results suggest that the H5N1 polymerase gene segments, and to a lesser extent the NS gene segment, contribute to cytokine hyperinduction in human macrophages and that a putative H5 pandemic virus that may arise through genetic reassortment between H5N1 and one of the current seasonal influenza viruses may have a markedly altered cytokine phenotype."

The full article can be found at: (K.P. Mok, et. al., "Viral Genetic Determinants of H5N1 Influenza Viruses That Contribute to Cytokine Dysregulation". Journal of Infectious Diseases, 2009;200(7):1104-1112). Link not available.
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T-CELL TOLERANCE FOR VARIABILITY IN AN HLA CLASS I-PRESENTED INFLUENZA A VIRUS EPITOPE
Biotech Law Weekly
October 23, 2009

"To escape immune recognition, viruses acquire amino acid substitutions in class I human leukocyte antigen (HLA)-presented cytotoxic T-lymphocyte (CTL) epitopes. Such viral escape mutations may (i) prevent peptide processing, (ii) diminish class I HLA binding, or (iii) alter T-cell recognition."

"Because residues 418 to 426 of the hypervariable influenza A virus nucleoprotein (NP418-426) epitope are consistently bound by class I HLA and presented to CTL, we assessed the impact that intraepitope sequence variability has upon T-cell recognition. CTL elicited by intranasal influenza virus infection were tested for their cross-recognition of 20 natural NP418-426 epitope variants. Six of the variant epitopes, of both H1N1 and H3N2 origin, were cross-recognized by CTL while the remaining NP418-426 epitope variants escaped targeting. A pattern emerged whereby variability at position 5 (P5) within the epitope reduced T-cell recognition, changes at P4 or P6 enabled CTL escape, and a mutation at P8 enhanced T-cell recognition."

"These data demonstrate that substitutions at P4 and/or P6 facilitate influenza virus escape from T-cell recognition and provide a model for the number, nature, and location of viral mutations that influence T-cell cross-recognition."

The full article can be found at: (A. Wahl, et. al., "T-Cell Tolerance for Variability in an HLA Class I-Presented Influenza A Virus Epitope". Journal of Virology, 2009;83(18):9206-9214). Link not available.
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EVALUATION OF AN EPITOPE-BLOCKING ENZYME-LINKED IMMUNOSORBENT ASSAY FOR THE DETECTION OF ANTIBODIES TO INFLUENZA A VIRUS IN DOMESTIC AND WILD AVIAN AND MAMMALIAN SPECIES
Drug Week
October 23, 2009

"An epitope-blocking enzyme-linked immunosorbent assay (bELISA) was developed for the detection of antibodies to influenza A virus in taxonomically diverse domestic and wild vertebrate species. In contrast to the bELISAs published previously that require reagent production, manipulation by the end-user, or have not been evaluated for use with both mammalian and avian species, this assay is performed using commercially available recombinant nucleoprotein antigen and corresponding nucleoprotein-specific monoclonal antibody and has been shown to work with multiple avian and mammalian species."

"The efficacy of the bELISA as a serum screening assay was compared to the agar gel immunodiffusion (AGID) assay using 251 serum samples obtained from experimentally infected mallards (Anas platyrhynchos) and raccoons (Procyon lotor). The concordance between the AGID assay and bELISA was 94.1% (95% Cl = 89.9. 98.3) for raccoons, and 71.2% (95% Cl = 63.5, 78.9) for mallards and 82.8% (95% Cl = 78.2, 87.3) overall. The bELISA was more sensitive than the AGID assay as demonstrated by the detection of antibodies to influenza A virus at earlier time points in experimental infection studies and at higher serial dilutions. The efficacy of the bELISA to monitor natural influenza A virus exposure was also compared to the AGID assay using an additional 745 serum samples from six avian species and six mammalian species."

"This bELISA provides a rapid, reliable, and inexpensive technique for large-scale surveillance of influenza A virus exposure in taxonomically diverse vertebrate species. ."

The full article can be found at: (Evaluation of an epitope-blocking enzyme-linked immunosorbent assay for the detection of antibodies to influenza A virus in domestic and wild avian and mammalian species. Journal of Virological Methods, 2009;161(1):141-146). Link not available.
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TARGETED VS. SYSTEMATIC EARLY ANTIVIRAL TREATMENT AGAINST A(H1N1)V INFLUENZA WITH NEURAMINIDASE INHIBITORS IN PATIENTS WITH INFLUENZA-LIKE SYMPTOMS: CLINICAL AND ECONOMIC IMPACT
By Sylvie Deuffic-Burban, Xavier Lenne, Benoit Dervaux, Julien Poissy, Xavier Lemaire, and Caroline Sloan
PloS Currents – Influenza
October 26, 2009

"Capitalizing on available data, we used a decision model to estimate the clinical and economic outcomes associated with early initiation of treatment with neuraminidase inhibitors in all patients with influenza-like illnesses (ILI) (systematic strategy) vs. only those at high risk of complications (targeted strategy). Systematic treatment of ILI during an A(H1N1)v influenza epidemic wave is both effective and cost-effective. Patients who present to care with ILI during an A(H1N1)v influenza epidemic wave should initiate treatment with neuraminidase inhibitors, regardless of risk status.

Administering neuraminidase inhibitors between epidemic waves, when the probability of influenza is low, is less effective and cost-effective."

.....

"Discussion

We used available data on the A(H1N1)v influenza epidemic in New Zealand to build a decision model and assess the clinical benefits and cost-effectiveness of different antiviral treatment strategies in the French population. Systematic initiation of neuraminidase inhibitors in patients who present to care with ILI during an A(H1N1)v influenza epidemic wave reduces mortality compared to a strategy that only targets patients at high risk of developing complications, and leads to a cost-effectiveness ratio of €4,100/YLG. According to the World Health Organization Commission on Macroeconomics and Health, an intervention is cost-effective if it delivers life years at a cost below three times the per capita Gross Domestic Product (GDP) (€91,240 for France in 2008) [43]. The systematic strategy falls well below this threshold. Clinical benefits and cost-effectiveness were sensitive to the probability of A(H1N1)v influenza in patients who present to care with ILI, the probability of hospitalization among A(H1N1)v-infected patients and, most importantly, oseltamivir efficacy. Clinical benefits were also sensitive to variations in the A(H1N1)v influenza attack rate and the probability of ICU admission given hospitalization……"

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"Variations in antiviral treatment efficacy had a large impact on results. When we decreased the efficacy of oseltamivir, the clinical benefits of systematic treatment decreased and cost-effectiveness ratios increased….."

.....

Results were sensitive to the probability of diagnosing A(H1N1)v influenza in patients with ILI. When this probability decreased, the systematic strategy became less effective and less cost-effective. When we set it to 5% and decreased oseltamivir efficacy, clinical benefits were small and cost-effectiveness ratios increased sharply. Given uncertainties surrounding the efficacy of neuraminidase inhibitors, and in the absence of rapid A(H1N1)v diagnostic tests that might reduce inappropriate neuraminidase inhibitor use, physicians should initiate antiviral treatment in all patients with ILI when A(H1N1)v reaches epidemic rates, but not between epidemic waves.

Mortality rates were especially sensitive to the A(H1N1)v influenza attack rate. When we increased the attack rate, mortality differences between the systematic strategy and the targeted strategy increased, but cost-effectiveness ratios remained stable. The attack rate in our analysis, derived from New Zealand data, is lower than predictions for upcoming A(H1N1)v epidemics. If A(H1N1)v influenza attack rates increase, the systematic strategy will be much more effective and cost-effectiveness ratios will remain stable.

This study has several limitations. First, our model combines input data from several sources and relies on several assumptions to estimate the impact of different antiviral treatment strategies. …... Second, the impact of neuraminidase inhibitors on complication rates is uncertain. Our results were robust to variations in treatment efficacy, except when the probability of diagnosing A(H1N1)v influenza in patients with ILI was low. Third, we did not account for oseltamivir-related adverse events, but these events are rare and it is unlikely that they would impact our results. Fourth, we did not account for resistance to oseltamivir, which could become more frequent as the availability of neuraminidase inhibitors increases. ….. In addition, we did not incorporate the economic benefits of stockpiling oseltamivir in preparation for an eventual influenza pandemic, as has been done in France and other countries. …... Finally, we did not consider the effects of A(H1N1)v influenza vaccination. The results of our study cannot be extrapolated to a vaccinated population because the severity of disease in vaccinated and unvaccinated populations may differ. However, it is likely that a large proportion of the general population in France will refuse to be vaccinated [55], and most countries have recommended vaccination for high-risk groups only [56][57]."

The full article can be found at: http://knol.google.com/k/sylvie-deuffic-burban/targeted-vs-systematic-early-antiviral/1vezxg5atvojv/2?collectionId=28qm4w0q65e4w.1&position=1
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FDA AUTHORIZES EMERGENCY USE OF INTRAVENOUS ANTIVIRAL PERAMIVIR FOR 2009 H1N1 INFLUENZA FOR CERTAIN PATIENTS, SETTINGS
Infection Control Today Magazine
October 26, 2009

"The Food and Drug Administration (FDA) announced today that, in response to a request from the Centers for Disease Control and Prevention (CDC), it has issued an emergency use authorization (EUA) for the investigational antiviral drug peramivir intravenous (IV) in certain adult and pediatric patients with confirmed or suspected 2009 H1N1 influenza infection who are admitted to a hospital.

Specifically, IV peramivir is authorized only for hospitalized adult and pediatric patients for whom therapy with an IV drug is clinically appropriate, based on one or more of the following reasons:

1.the patient is not responding to either oral or inhaled antiviral therapy, or

2.when drug delivery by a route other than an intravenous route -- e.g., enteral (absorbed by the intestines) or inhaled -- is not expected to be dependable or feasible;

3.for adults only, when the clinician judges IV therapy is appropriate due to other circumstances.

The FDA has reviewed the available scientific data and has concluded that the criteria for authorizing the emergency use of IV peramivir have been met.

There are no FDA-approved intravenously administered antivirals for the treatment of influenza. Peramivir is the only intravenously administered influenza treatment currently authorized for use under EUA for 2009 H1N1 infections.

The EUA authority allows the FDA, based on the evaluation of available data, to authorize the use of unapproved or uncleared medical products or unapproved or uncleared uses of approved or cleared medical products following a determination and declaration of emergency, provided certain criteria are met. The authorization will end when the declaration of emergency is terminated or the authorization is revoked by the agency."

The full article can be found at: http://www.infectioncontroltoday.com/hotnews/intravenous-antiviral-peramivir-h1n1-flu.html
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INFLUENZA PANDEMIC (H1N1) 2009 (76): EL SALVADOR, DENGUE CO-INFECTION
PreMED-mail
October 24, 2009

"In the eastern zone of the country, there have been reports of patients with simultaneous infection [co-infection] of influenza A (H1N1) and classical dengue fever, confirmed by the Vice Minister of Health, Eduardo Espinoza. In total, there have been 4 such cases of co-infection in the country nationwide."

.....

"The Vice Minister of Health, Violeta Menjivar, does not believe that there will be an intersection of the

disease at the national level, because preventive sanitary measures have been implemented and reinforced, and there is a focus on identifying and finding preventive processes.

Communication with Honduras has been established in order to implement joint sanitary policies and avoid a major outbreak related to the flow of people, she said."

The full article can be found at: http://www.promedmail.org/pls/otn/f?p=2400:1001:4230844457742528::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1000,79805
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