

20 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 #83**

### **1. FDA WARNS OF ILLEGAL H1N1 DRUG PRODUCTS PURCHASED OVER THE**

**INTERNET:** *“One of the orders, which arrived in an unmarked envelope with a postmark from India, consisted of unlabeled, white tablets taped between two pieces of paper. When analyzed by the FDA, the tablets were found to contain talc and acetaminophen, but none of the active ingredient oseltamivir.”*

### **2. CHEST RADIOGRAPHIC AND CT FINDINGS IN NOVEL SWINE-ORIGIN**

**INFLUENZA A (H1N1) VIRUS (S-OIV) INFECTION:** *“Chest radiographs are normal in more than half of patients with S-OIV (H1N1) and progress to bilateral extensive air-space disease in severely ill patients, who are at a high risk for PE [pulmonary embolism].”*

### **3. PSORIASIS PATIENTS TAKING IMMUNOSUPPRESSIVE DRUGS AT INCREASED**

**RISK OF H1N1 FLU VIRUSES:** *“People with psoriasis and/or psoriatic arthritis who are taking biologic or non-biologic immunosuppressive medications should receive the inactivated forms of both seasonal influenza and H1N1 (swine flu) vaccines as soon as possible, according to a recommendation from the National Psoriasis Foundation.”*

### **4. GIVING BABIES TYLENOL MAY BLUNT VACCINES' EFFECTS:**

*“It is the first major study to tie reduced immunity to the use of fever-lowering medicines. Although the effect was small and the vast majority of kids still got enough protection from vaccines, the results make “a compelling case” against routinely giving Tylenol right after vaccination, say doctors from the U.S. Centers for Disease Control and Prevention.”*

### **5. JAPAN VACCINATES MEDICAL WORKERS AGAINST PANDEMIC H1N1 SWINE**

**FLU:** *“Japan started vaccinating doctors and other health professionals against H1N1 swine flu on Monday, following a government decision to prioritize recipients of the limited vaccine supply which is being produced in Japan.”*

### **6. GREEN TEA CATECHINS INHIBIT THE ENDONUCLEASE ACTIVITY OF INFLUENZA**

**A VIRUS RNA POLYMERASE:** *“The influenza A RNA polymerase possesses endonuclease activity to digest the host mRNA. Thus this endonuclease domain can be a target of anti-influenza A virus drug. Here we report that green tea catechins inhibit this viral endonuclease activity and that their galloyl group is important for their function. Docking*

*simulations revealed that catechins with galloyl group fit well into the active pocket of the endonuclease domain to enable stable binding. Our results provide useful data that make it possible to refine and optimize catechin-based drug design more readily for stability."*

**7. OPTIMIZING INFLUENZA VACCINE DISTRIBUTION:** *"We also found that previous and new recommendations from the U. S. Centers for Disease Control and Prevention both for the novel swine-origin influenza and, particularly, for seasonal influenza, are suboptimal for all outcome measures."*

## CB Daily Report

### Chem-Bio News

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#### **FDA WARNS OF ILLEGAL H1N1 DRUG PRODUCTS PURCHASED OVER THE INTERNET**

Infection Control Today Magazine

October 16, 2009

"The Food and Drug Administration (FDA) today warned consumers to use extreme care when purchasing any products over the Internet that claim to diagnose, prevent, treat or cure the H1N1 influenza virus. The warning comes after the FDA recently purchased and analyzed several products represented online as Tamiflu (oseltamivir), which may pose risks to patients.

One of the orders, which arrived in an unmarked envelope with a postmark from India, consisted of unlabeled, white tablets taped between two pieces of paper. When analyzed by the FDA, the tablets were found to contain talc and acetaminophen, but none of the active ingredient oseltamivir. The Web site disappeared shortly after the FDA placed the order. At the same time, the FDA also purchased four other products purported to diagnose, prevent, treat or cure the H1N1 influenza virus from other Web sites.

These products contained various levels of oseltamivir but were not approved for use in the United States. Several of the products purchased did not require a prescription from a healthcare professional. Additionally, the products did not arrive in a timely enough fashion to treat someone infected with the H1N1 influenza virus, or with an immediate exposure to the virus."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/fda-warns-of-illegal-flu-drugs.html>

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#### **CHEST RADIOGRAPHIC AND CT FINDINGS IN NOVEL SWINE-ORIGIN INFLUENZA A (H1N1) VIRUS (S-OIV) INFECTION**

By Prachi P. Agarwal, Sandro Cinti, and Ella A. Kazerooni

American Journal of Roentgenology

December 2009

“Objective. This article reviews the chest radiographic and CT findings in patients with presumed/laboratory-confirmed novel swine-origin influenza A (H1N1) virus (S-OIV) infection.

Materials and Methods. Of 222 patients with novel S-OIV (H1N1) infection seen from May 2009 to July 2009, 66 patients (30%) who underwent chest radiographs formed the study population. Group 1 patients (n = 14) required ICU admission and advanced mechanical ventilation, and group 2 (n = 52) did not. The initial radiographs were evaluated for the pattern (consolidation, ground-glass, nodules, and reticulation), distribution, and extent of abnormality. Chest CT scans (n = 15) were reviewed for the same findings and for pulmonary embolism (PE) when performed using IV contrast medium.

Results. Group 1 patients were predominantly male with a higher mean age (43.5 years versus 22.1 years in group 2;  $p < 0.001$ ). The initial radiograph was abnormal in 28 of 66 (42%) subjects. The predominant radiographic finding was patchy consolidation (14/28; 50%) most commonly in the lower (20/28; 71%) and central lung zones (20/28; 71%). All group 1 patients had abnormal initial radiographs; extensive disease involving  $\geq 3$  lung zones was seen in 93% (13/14) versus 9.6% (5/52) in group 2 ( $p < 0.001$ ). No group 2 patients had  $>20\%$  overall lung involvement on initial radiographs compared with 93% of group 1 patients (13/14). PEs were seen on CT in 5/14 (36%) of group 1 patients.

Conclusion. Chest radiographs are normal in more than half of patients with S-OIV (H1N1) and progress to bilateral extensive air-space disease in severely ill patients, who are at a high risk for PE.”

The full article can be found at: [http://www.ajronline.org/aheadofprint/12\\_09\\_3599.pdf](http://www.ajronline.org/aheadofprint/12_09_3599.pdf)

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## **PSORIASIS PATIENTS TAKING IMMUNOSUPPRESSIVE DRUGS AT INCREASED RISK OF H1N1 FLU VIRUSES**

The Medical News

October 13, 2009

“People with psoriasis and/or psoriatic arthritis who are taking biologic or non-biologic immunosuppressive medications should receive the inactivated forms of both seasonal influenza and H1N1 (swine flu) vaccines as soon as possible, according to a recommendation from the National Psoriasis Foundation.

The National Psoriasis Foundation's medical experts recommend that patients taking immunosuppressive medication including biologic (Amevive, Enbrel, Humira, Remicade, Simponi or Stelara) or non-biologic (cyclosporine-Neoral or methotrexate) drugs take the following steps:

- Get vaccinated early. The same medications that suppress psoriasis make patients

more vulnerable to influenza viruses.

- Receive both vaccines to be protected from seasonal and H1N1 flu viruses.
  - Receive only inactive vaccines. Both vaccines come in inactivated and live forms. People taking immunosuppressive medication should only receive the inactivated vaccines.
- Take more daily health precautions. The Centers for Disease Control (CDC) recommends avoiding close contact with people who are sick, washing hands frequently, and avoiding touching the eyes, nose and mouth."

The full article can be found at: <http://www.news-medical.net/news/20091013/Psoriasis-patients-taking-immunosuppressive-drugs-at-increased-risk-of-H1N1-flu-viruses.aspx>

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## **GIVING BABIES TYLENOL MAY BLUNT VACCINES' EFFECTS**

Physorg.com

October 15, 2009

"It is the first major study to tie reduced immunity to the use of fever-lowering medicines. Although the effect was small and the vast majority of kids still got enough protection from vaccines, the results make "a compelling case" against routinely giving Tylenol right after vaccination, say doctors from the U.S. Centers for Disease Control and Prevention.

They wrote an editorial accompanying the study, published in Friday's issue of the British medical journal, Lancet.

The study only looked at preventive use of Tylenol - not whether it is OK to use after a fever develops."

The full article can be found at: <http://www.physorg.com/news174850965.html>

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## **JAPAN VACCINATES MEDICAL WORKERS AGAINST PANDEMIC H1N1 SWINE FLU**

Medical News Today

October 19, 2009

"Japan started vaccinating doctors and other health professionals against H1N1 swine flu on Monday, following a government decision to prioritize recipients of the limited vaccine supply which is being produced in Japan.

According to a report by Tokyo-based online newspaper Japan Today, 1 million or so medical workers will be receiving the vaccine, followed by pregnant women and people with certain chronic diseases from November."

The full article can be found at: <http://www.medicalnewstoday.com/articles/167832.php>

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## **GREEN TEA CATECHINS INHIBIT THE ENDONUCLEASE ACTIVITY OF INFLUENZA A VIRUS RNA POLYMERASE**

By Takashi Kuzuhara, Yuma Iwai, and Hironobu Takahashi

PLoS Currents Influenza

October 14, 2009

“The influenza A RNA polymerase possesses endonuclease activity to digest the host mRNA. Thus this endonuclease domain can be a target of anti-influenza A virus drug. Here we report that green tea catechins inhibit this viral endonuclease activity and that their galloyl group is important for their function. Docking simulations revealed that catechins with galloyl group fit well into the active pocket of the endonuclease domain to enable stable binding. Our results provide useful data that make it possible to refine and optimize catechin-based drug design more readily for stability.”

### “Introduction

“In 1918, a pandemic expansion of influenza A virus killed more than 10 million people worldwide [1] and the prevention of future expansions of this virus is therefore an important endeavor. The emergence of new swine-origin H1N1 influenza A this year emphasizes this further as it represents a serious global health issue [2]. For the prevention and control of such new influenza outbreaks, the development of new antiviral drugs is critical [2]. Although inhibitors of neuraminidase are widely used as anti-influenza A drugs, some adverse effects of these agents and also the emergence of drug-resistant viruses have now been reported [3][4]. The influenza A virus genome comprises a negative RNA strand, the transcription and replication of which requires the activity of an RNA-dependent RNA polymerase [5]. This viral enzyme is highly conserved and thus represents a very promising target for anti-viral drug development. The influenza A virus RNA-dependent RNA polymerase is composed of three subunits, PA, PB1 and PB2 [6][7][8], and synthesizes viral mRNAs using short capped primers derived from host cellular pre-mRNAs. These molecules are cleaved after 10-13 nucleotides by an endonuclease in the N-terminal domain of the PA subunit. This unique endonuclease activity is thus essential for the influenza virus to propagate and should also be regarded as a potentially important target for anti-viral drug design. Yuan et al. and Dias et al. have recently shown that the N-terminal domain of the PA subunit contains the endonuclease active site in its tertiary structure and that this domain also has RNA and DNA endonuclease activity [6][8]. This reported information regarding the tertiary structure of PA can be used to refine possible endonuclease inhibitor candidates.

Green tea is a popular and healthy beverage in Japan. Most of the active components of green tea are assumed to be the catechins, because they have been shown to possess a variety of properties in in vitro cell cultures and also in vivo, including anti-oxidant, anti-cancer and DNA-binding activities [9][10]. (-)-Epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), (-)-epicatechin (EC), (-)-gallocatechin gallate (GCG) and (+)-catechin are the major components of green tea polyphenols [9], and

EGCG is one of the major components of green tea catechins (chemical structures are shown in Fig. 1) [9]. In addition, Song et al., have reported that EGCG at relatively high doses is an inhibitor of influenza A virus replication and also of viral RNA synthesis in cells [11]. They concluded from these findings that the antiviral effects of catechins on influenza are mediated via alterations in the physical properties of the viral membrane [11]. However, it has not yet been demonstrated how to refine and to optimize EGCG for use as an anti-influenza viral drug. The objective of this study is to investigate whether green tea catechins inhibit influenza A virus endonuclease and which chemical groups of catechin are important for this activity. In this study, we report that the several kinds of green tea catechins can inhibit the endonuclease activity of the PA subunit of the influenza A virus and be refined for a candidate of the anti-viral drug through in silico calculation."

The full article can be found at: <http://knol.google.com/k/takashi-kuzuhara/green-tea-catechins-inhibit-the/1yn7909cwn80/2?collectionId=28qm4w0q65e4w.1&position=1#>

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## **OPTIMIZING INFLUENZA VACCINE DISTRIBUTION**

Preventive Medicine Week

October 25, 2009

"The criteria to assess public health policies are fundamental to policy optimization. Using a model parametrized with survey-based contact data and mortality data from influenza pandemics, we determined optimal vaccine allocation for five outcome measures: deaths, infections, years of life lost, contingent valuation, and economic costs."

"We find that optimal vaccination is achieved by prioritization of schoolchildren and adults aged 30 to 39 years. Schoolchildren are most responsible for transmission, and their parents serve as bridges to the rest of the population. Our results indicate that consideration of age-specific transmission dynamics is paramount to the optimal allocation of influenza vaccines."

"We also found that previous and new recommendations from the U. S. Centers for Disease Control and Prevention both for the novel swine-origin influenza and, particularly, for seasonal influenza, are suboptimal for all outcome measures."

The full article can be found at: (J. Medlock, et. al., "Optimizing Influenza Vaccine Distribution". Science, 2009; 325(5948): 1705-1708). Link not available.

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