

27 January 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 #45**

### **1. NOVAVAX ANNOUNCES OPERATIONAL STATUS OF ITS VACCINE PILOT PLANT AND COMMERCIAL LAUNCH FACILITY:**

*“Novavax, Inc. announced today that all equipment in its new Good Manufacturing Practice (“GMP”) Pilot Plant to manufacture pandemic and seasonal influenza vaccine clinical supplies and commercial batches at a 1,000 liter scale are installed and ready for operations supporting scale-up and validation.”*

### **2. WHO SHOULD RECEIVE LIFE SUPPORT DURING A PUBLIC HEALTH EMERGENCY? USING ETHICAL PRINCIPLES TO IMPROVE ALLOCATION DECISIONS:**

*“We analyze the ethical principles that could guide allocation and propose an allocation strategy that incorporates and balances multiple morally relevant considerations, including saving the most lives, maximizing the number of “life-years” saved, and prioritizing patients who have had the least chance to live through life’s stages.”*

### **3. ANTIVIRAL RESISTANCE DURING PANDEMIC INFLUENZA: IMPLICATIONS FOR STOCKPILING AND DRUG USE:**

*“We applied an antiviral strategy that delays the onset of aggressive treatment for a certain amount of time after the onset of the outbreak.”*

### **4. CD4(+) AND CD8(+) T CELLS EXHIBIT DIFFERENTIAL REQUIREMENTS FOR CCR7-MEDIATED ANTIGEN TRANSPORT DURING INFLUENZA INFECTION:**

*“We found that CCR7-mediated migration of dendritic cells was more crucial for CD8(+) T cell than CD4(+) T cell responses.”*

### **5. X-RAY STRUCTURE OF NS1 FROM A HIGHLY PATHOGENIC H5N1 INFLUENZA VIRUS:**

*“The tubular oligomeric organization of NS1, in which residues implicated in dsRNA binding face a 20-angstrom-wide central tunnel, provides a plausible mechanism for how NS1 sequesters varying lengths of dsRNA, to counter cellular antiviral dsRNA response pathways, while simultaneously interacting with other cellular ligands during an infection.”*

### **6. MULTIPLE GLYCINES IN TCR ALPHA-CHAINS DETERMINE CLONALLY DIVERSE NATURE OF HUMAN T CELL MEMORY TO INFLUENZA A VIRUS:**

*“A unique feature of these alpha TCRs was the presence of CDR3 fitting to an AGA(G(n))GG-like amino acid*

motif."

# CB Daily Report

## Chem-Bio News

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### **NOVAVAX ANNOUNCES OPERATIONAL STATUS OF ITS VACCINE PILOT PLANT AND COMMERCIAL LAUNCH FACILITY**

Bio-Medicine.org  
January 26, 2009

"Novavax, Inc. announced today that all equipment in its new Good Manufacturing Practice ("GMP") Pilot Plant to manufacture pandemic and seasonal influenza vaccine clinical supplies and commercial batches at a 1,000 liter scale are installed and ready for operations supporting scale-up and validation."

"The facility is expected to be capable of producing 2-3 million doses of monovalent pandemic influenza vaccine per week at 15 mcg HA/dose (50 - 75 M doses in 6 months) once scale-up and validation are complete. Likewise, the facility can support up to 20 - 25 million doses of trivalent influenza vaccine in six months. The facility is GMP compliant and includes a total of 10,000 square feet of production and support space. The facility also includes media and reagent preparation space and equipment for production of vaccine for clinical trials. Large-scale commercial production, media, reagent and filling of bulk vaccines are planned to be outsourced."

The full article can be found at: <http://www.bio-medicine.org/biology-technology-1/Novavax-Announces-Operational-Status-of-Its-Vaccine-Pilot-Plant-and-Commercial-Launch-Facility-10103-1/>

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### **WHO SHOULD RECEIVE LIFE SUPPORT DURING A PUBLIC HEALTH EMERGENCY? USING ETHICAL PRINCIPLES TO IMPROVE ALLOCATION DECISIONS**

By Douglas B. White, MD, MAS; Mitchell H. Katz, MD; John M. Luce, MD; and Bernard Lo, MD  
Annals of Internal Medicine  
January 20, 2009

"A public health emergency, such as an influenza pandemic, will lead to shortages of mechanical ventilators, critical care beds, and other potentially life-saving treatments. Difficult decisions about who will and will not receive these scarce resources will have to be made. Existing recommendations reflect a narrow utilitarian perspective, in which allocation decisions are based primarily on patients' chances of survival to hospital discharge. Certain patient groups, such as the elderly and those with functional impairment, are denied access to potentially life-saving treatments on the basis of additional allocation criteria. We analyze

the ethical principles that could guide allocation and propose an allocation strategy that incorporates and balances multiple morally relevant considerations, including saving the most lives, maximizing the number of "life-years" saved, and prioritizing patients who have had the least chance to live through life's stages. We also argue that these principles are relevant to all patients and therefore should be applied to all patients, rather than selectively to the elderly, those with functional impairment, and those with certain chronic conditions. We discuss strategies to engage the public in setting the priorities that will guide allocation of scarce life-sustaining treatments during a public health emergency."

The full article can be found at: <http://www.annals.org/cgi/content/abstract/150/2/132>

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## **ANTIVIRAL RESISTANCE DURING PANDEMIC INFLUENZA: IMPLICATIONS FOR STOCKPILING AND DRUG USE**

By Julien Arino, Christopher S Bowman, and Seyed M Moghadas

BMC Infectious Diseases

January 22, 2009

"Results

We demonstrated that the emergence of highly transmissible resistant strains has no significant impact on the use of available stockpiles if treatment is maintained at low levels or the reproduction number of the sensitive strain is sufficiently high. However, moderate to high treatment levels can result in a more rapid depletion of stockpiles, leading to run-out, by promoting wide-spread drug resistance. We applied an antiviral strategy that delays the onset of aggressive treatment for a certain amount of time after the onset of the outbreak. Our results show that if high treatment levels are enforced too early during the outbreak, a second wave of infections can potentially occur with a substantially larger magnitude. However, a timely implementation of wide-scale treatment can prevent resistance spread in the population, and minimize the final size of the pandemic.

Conclusions

Our results reveal that conservative treatment levels during the early stages of the outbreak, followed by a timely increase in the scale of drug-use, will offer an effective strategy to manage drug resistance in the population and avoid run-out. For a 1918-like strain, the findings suggest that pandemic plans should consider stockpiling antiviral drugs to cover at least 20% of the population."

The full article can be found at: <http://www.biomedcentral.com/1471-2334/9/8>

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## **CD4(+) AND CD8(+) T CELLS EXHIBIT DIFFERENTIAL REQUIREMENTS FOR CCR7-MEDIATED ANTIGEN TRANSPORT DURING INFLUENZA INFECTION**

"Upon encounter of viral Ags in an inflammatory environment, dendritic cells up-regulate costimulatory molecules and the chemokine receptor CCR7, with the latter being pivotal for their migration to the lymph node. By utilizing mice deficient in CCR7, we have examined the requirement of dendritic cell-mediated Ag transport from the lung to the draining lymph node for the induction of anti-influenza immune responses *in vivo*."

"We found that CCR7-mediated migration of dendritic cells was more crucial for CD8(+) T cell than CD4(+) T cell responses. While no specific CD8(+) T cell response could be detected in the airways or lymphoid tissues during the primary infection, prolonged infection in CCR7-deficient mice did result in a sustained inflammatory chemokine profile, which led to nonspecific CD8(+) T cell recruitment to the airways. The recruitment of influenza-specific CD4+ T cells to the airways was also below levels of detection in the absence of CCR7 signaling, although a small influenza-specific CD4(+) T cell population was detectable in the draining lymph node, which was sufficient for the generation of class-switched anti-influenza Abs and a normal CD4(+) T cell memory population. Overall, our data show that CCR7-mediated active Ag transport is differentially required for CD4(+) and CD8(+) T cell expansion during influenza infection."

The full article can be found at: (A.K. Heer, et. al., "CD4(+) and CD8(+) T Cells Exhibit Differential Requirements for CCR7-Mediated Antigen Transport during Influenza Infection". *Journal of Immunology*, 2008; 181(10):6984-6994). Link not available.

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## **X-RAY STRUCTURE OF NS1 FROM A HIGHLY PATHOGENIC H5N1 INFLUENZA VIRUS**

Drug Week

January 23, 2009

"The recent emergence of highly pathogenic avian (H5N1) influenza viruses, their epizootic and panzootic nature, and their association with lethal human infections have raised significant global health concerns(1,2). Several studies have underlined the importance of non-structural protein NS1 in the increased pathogenicity and virulence of these strains (3,4)."

"NS1, which consists of two domains a double-stranded RNA (dsRNA) binding domain(5,6) and the effector domain(7), separated through a linker - is an antagonist of antiviral type-I interferon response in the host(8,9). Here we report the X-ray structure of the full-length NS1 from an H5N1 strain (A/Vietnam/1203/2004) that was associated with 60% of human deaths in an outbreak in Vietnam(1,2). Compared to the individually determined structures of the RNA binding domain and the effector domain from non-H5N1 strains, the RNA binding domain within H5N1 NS1 exhibits modest structural changes, while the H5N1 effector domain shows significant alteration, particularly in the dimeric interface. Although both domains in the full-length NS1 individually participate in dimeric interactions, an unexpected finding is that these interactions result in the formation of a chain of NS1

molecules instead of distinct dimeric units. Three such chains in the crystal interact with one another extensively to form a tubular organization of similar dimensions to that observed in the cryo- electron microscopy images of NS1 in the presence of dsRNA."

"The tubular oligomeric organization of NS1, in which residues implicated in dsRNA binding face a 20-angstrom-wide central tunnel, provides a plausible mechanism for how NS1 sequesters varying lengths of dsRNA, to counter cellular antiviral dsRNA response pathways, while simultaneously interacting with other cellular ligands during an infection."

The full article can be found at: (Z.A. Bornholdt, et. al., "X-ray structure of NS1 from a highly pathogenic H5N1 influenza virus". Nature, 2008; 456(7224):985-U85). Link not available.

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## **MULTIPLE GLYCINES IN TCR ALPHA-CHAINS DETERMINE CLONALLY DIVERSE NATURE OF HUMAN T CELL MEMORY TO INFLUENZA A VIRUS**

Medical Devices & Surgical Technology Week  
January 25, 2009

"Using molecular cloning, we systematically studied the impact of alpha-chain usage in the formation of T cell memory and revealed that M1(58-56)-specific, clonally diverse VB19 T cells express alpha-chains encoded by multiple AV genes with different CDR3 sizes. A unique feature of these alpha TCRs was the presence of CDR3 fitting to an AGA(G(n))GG-like amino acid motif. This pattern was consistent over time and among different individuals. Further molecular assessment of human CD4(+)CD8(-) and CD4(-)CD8(+) thymocytes led to the conclusion that the poly-Gly/Ala runs in CDR3 alpha were a property of immune, but not naive, repertoires and could be attributed to influenza exposure. Repertoires of T cell memory are discussed in the context of clonal diversity, where poly-Gly/Ala runs in the CDR3 of alpha- and beta-chains might provide high levels of TCR flexibility during Ag recognition while gene-encoded CDR1 and CDR2 contribute to the fine specificity of the TCR-peptide MHC interaction."

The full article can be found at: (Y.N. Naumov, et. al., "Multiple Glycines in TCR alpha-Chains Determine Clonally Diverse Nature of Human T Cell Memory to Influenza A Virus". Journal of Immunology, 2008; 181(10):7407-7419). Link not available.

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