

26 May 2009

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## **Chem-Bio News – Pandemic Influenza Edition #62**

- 1. HEDGING AGAINST ANTIVIRAL RESISTANCE DURING THE NEXT INFLUENZA PANDEMIC USING SMALL STOCKPILES OF AN ALTERNATIVE CHEMOTHERAPY:** *“Our results indicate that the augmentation of existing stockpiles of a single anti-influenza drug with smaller stockpiles of a second drug could be an effective and inexpensive epidemiological hedge against antiviral resistance if either SMC [sequential multidrug chemotherapy] or ECC [early combination chemotherapy] were used.”*
- 2. WHO CHIEF TO SEEK DEAL ON SHARING FLU VIRUS SAMPLES:** *“Countries facing an imminent flu pandemic are making progress on an agreement on how to share drugs, vaccines and the viruses needed to make them, the head of the World Health Organization said on Thursday.”*
- 3. WHO CHIEF WARNS H1N1 SWINE FLU LIKELY TO WORSEN:** *“A genetic analysis of the new virus showed it must have been circulating undetected for some time, in pigs or perhaps in other animals.”*
- 4. INVESTIGATORS UNCOVER HOW FLU VIRUS ELUDES THE BODY'S DEFENSES:** *“Researchers at the University of Southern California (USC) identified a molecular mechanism that allows the influenza virus to evade the body's immune response system.”*
- 5. WHO, GSK [GLAXOSMITHKLINE] PROVIDE UPDATE ON PANDEMIC FLU PRODUCTION:** *“A review of 2009 production status for the Northern Hemisphere seasonal vaccine indicates that the industry plans to produce approximately 480 million doses of trivalent seasonal vaccine in 2009, according to a statement by the World Health Organization Working Group.”*
- 6. SERUM CROSS-REACTIVE ANTIBODY RESPONSE TO A NOVEL INFLUENZA A (H1N1) VIRUS AFTER VACCINATION WITH SEASONAL INFLUENZA VACCINE:** *“The results in this report suggest that vaccination with recent (2005--2009) seasonal influenza vaccines is unlikely to provide protection against the novel influenza A (H1N1) virus.”*

# **CB Daily Report**

## **Chem-Bio News**

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### **HEDGING AGAINST ANTIVIRAL RESISTANCE DURING THE NEXT INFLUENZA PANDEMIC USING SMALL STOCKPILES OF AN ALTERNATIVE CHEMOTHERAPY**

By Joseph T. Wu, Gabriel M. Leung, Marc Lipsitch, Ben S. Cooper, Steven Riley  
PLoS Medicine  
May 19, 2009

“Background

The effectiveness of single-drug antiviral interventions to reduce morbidity and mortality during the next influenza pandemic will be substantially weakened if transmissible strains emerge which are resistant to the stockpiled antiviral drugs. We developed a mathematical model to test the hypothesis

that a small stockpile of a secondary antiviral drug could be used to mitigate the adverse consequences of the emergence of resistant strains.

## Methods and Findings

We used a multistrain stochastic transmission model of influenza to show that the spread of antiviral resistance can be significantly reduced by deploying a small stockpile (1% population coverage) of a secondary drug during the early phase of local epidemics. We considered two strategies for the use of the secondary stockpile: early combination chemotherapy (ECC; individuals are treated with both drugs in combination while both are available); and sequential multidrug chemotherapy (SMC; individuals are treated only with the secondary drug until it is exhausted, then treated with the primary drug). We investigated all potentially important regions of unknown parameter space and found that both ECC and SMC reduced the cumulative attack rate (AR) and the resistant attack rate (RAR) unless the probability of emergence of resistance to the primary drug  $p_A$  was so low (less than 1 in 10,000) that resistance was unlikely to be a problem or so high (more than 1 in 20) that resistance emerged as soon as primary drug monotherapy began. For example, when the basic reproductive number was 1.8 and 40% of symptomatic individuals were treated with antivirals, AR and RAR were 67% and 38% under monotherapy if  $p_A = 0.01$ . If the probability of resistance emergence for the secondary drug was also 0.01, then SMC reduced AR and RAR to 57% and 2%. The effectiveness of ECC was similar if combination chemotherapy reduced the probabilities of resistance emergence by at least ten times. We extended our model using travel data between 105 large cities to investigate the robustness of these resistance-limiting strategies at a global scale. We found that as long as populations that were the main source of resistant strains employed these strategies (SMC or ECC), then those same strategies were also effective for populations far from the source even when some intermediate populations failed to control resistance. In essence, through the existence of many wild-type epidemics, the interconnectedness of the global network dampened the international spread of resistant strains.

## Conclusions

Our results indicate that the augmentation of existing stockpiles of a single anti-influenza drug with smaller stockpiles of a second drug could be an effective and inexpensive epidemiological hedge against antiviral resistance if either SMC or ECC were used. Choosing between these strategies will require additional empirical studies. Specifically, the choice will depend on the safety of combination therapy and the synergistic effect of one antiviral in suppressing the emergence of resistance to the other antiviral when both are taken in combination."

The full article can be found at: <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000085>

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## **WHO CHIEF TO SEEK DEAL ON SHARING FLU VIRUS SAMPLES**

By Laura MacInnis

Reuters

May 21, 2009

"Countries facing an imminent flu pandemic are making progress on an agreement on how to share drugs, vaccines and the viruses needed to make them, the head of the World Health Organization said on Thursday.

Director-General Margaret Chan told officials at the WHO's annual meeting that collaboration seen between governments, drug makers and vaccine makers since the emergence of the H1N1 strain gave hope for conciliation between rich and poor countries."

The biggest sticking point in those talks has been how and when biological samples of viruses would be shared with the world's pharmaceutical companies who need them to make vaccines, an issue known as "material transfer."

Indonesia and other developing countries have been pushing for guarantees that vaccines developed from such virus samples they provide will be made available at an affordable price, and in sufficient quantities to protect poorer nations.”

The full article can be found at: <http://www.reuters.com/article/healthNews/idUSTRE54K2EB20090521>  
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### **WHO CHIEF WARNS H1N1 SWINE FLU LIKELY TO WORSEN**

By Laura MacInnis and Stephanie Nebehay

Reuters

May 22, 2009

“A genetic analysis of the new virus showed it must have been circulating undetected for some time, in pigs or perhaps in other animals.

The WHO is poised to declare a full pandemic of the virus, which has infected more than 11,000 people in 42 countries and killed 86. And U.S. health officials released \$1 billion for companies to get started on a vaccine in case it is needed.

The virus must be closely monitored in the southern hemisphere, as it could mix with ordinary seasonal influenza and change in unpredictable ways, Chan told the WHO annual congress in Geneva.”

“An international team of researchers who analyzed all eight genes of the new virus confirmed its sneakiness, saying it was so different from its ancestral strains that it must have been circulating undetected for years.”

The full article can be found at: <http://www.alertnet.org/thenews/newsdesk/N22387871.htm>  
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### **INVESTIGATORS UNCOVER HOW FLU VIRUS ELUDES THE BODY'S DEFENSES**

Genetic Engineering & Biotechnology News

May 21, 2009

“Researchers at the University of Southern California (USC) identified a molecular mechanism that allows the influenza virus to evade the body's immune response system. The virus' nonstructural protein 1 (NS1) targets a particular ubiquitin ligase to hide from the host viral RNA sensor.

The influenza A virus has evolved the NS1 protein into its genome to escape the immune system, but the precise process it uses has been unclear. “We now know that the influenza virus escapes recognition via the interaction of NS1 with TRIM25, which inhibits the body's immune response,” explains Jae Jung, Ph.D., professor and chair of the department of molecular microbiology and immunology at the Keck School of Medicine of USC.”

The full article can be found at: <http://www.genengnews.com/news/bnitem.aspx?name=54942268>  
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### **WHO, GSK [GLAXOSMITHKLINE] PROVIDE UPDATE ON PANDEMIC FLU PRODUCTION**

PharmTech.com

May 21, 2009

“A review of 2009 production status for the Northern Hemisphere seasonal vaccine indicates that the industry plans to produce approximately 480 million doses of trivalent seasonal vaccine in 2009,

according to a statement by the World Health Organization Working Group. Of this amount, 350 million and 430 million doses will be available by June 30 and July 31, 2009, respectively. For influenza A (H1N1), it is estimated that up to 4.9 billion doses could be produced over a 12-month period after the initiation of full-scale production if there is a vaccine yield equivalent to that routinely obtained for seasonal vaccine and if the most dose-sparing formulations are used. In this situation, there is potential access for the United Nations of up to 400 million doses.

The WHO Working Group said it was premature to recommend that commercial-scale production of influenza A (H1N1) vaccine should start immediately but recommended the following actions:

- The WHO Secretariat, in close coordination with its Collaborating Centers and the Essential Regulatory Laboratories of the WHO Global Influenza Surveillance Network, should recommend which vaccine viruses should be used for vaccine development as soon as possible
- Essential reagents to calibrate antigenic content should be made available as a priority
- The WHO Secretariat is encouraged to collaborate actively with its Collaborating Centers, Essential Regulatory Laboratories, and with industry, to assess the growth property of vaccine viruses and identify those with best growth potential to maximize output of a vaccine
- Manufacturers are urged to develop clinical-trial batches and accelerate initiation of clinical trials of influenza A (H1N1) vaccines and to start preparing for potential future recommendations to move to commercial-scale production
- Present production of the Northern Hemisphere seasonal vaccine should not be interfered with by activities relating to pandemic preparedness

The full article can be found at: <http://pharmtech.findpharma.com/pharmtech/Manufacturing/WHO-GSK-Provide-Update-on-Pandemic-Flu-Production/ArticleStandard/Article/detail/599059?contextCategoryId=35097>

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## **SERUM CROSS-REACTIVE ANTIBODY RESPONSE TO A NOVEL INFLUENZA A (H1N1) VIRUS AFTER VACCINATION WITH SEASONAL INFLUENZA VACCINE**

MMWR (US Centers for Disease Control and Prevention)

May 21, 2009

“The results in this report suggest that vaccination with recent (2005--2009) seasonal influenza vaccines is unlikely to provide protection against the novel influenza A (H1N1) virus. Although vaccination of adults with seasonal TIV generally resulted in a small increase in antibodies against the novel influenza A (H1N1) virus, whether such levels of cross-reactive antibody provide any protection against infection with novel influenza A (H1N1) virus is unknown. These results are consistent with the substantial degree of genetic divergence of the novel influenza A (H1N1) virus of swine origin from recent seasonal human H1N1 viruses; A/California/04/09 shares only 72%--73% amino acid identity in the HA1 portion of the hemagglutinin molecule with the seasonal viruses used in this study. For comparison, the amino acid sequence identity in the HA1 portion among seasonal vaccine strains used in this study is 97%--98%.

Although the number of sera from children tested in this analysis was small, results indicate that U.S. children are largely serologically naïve to the novel influenza A (H1N1) virus and that vaccination with seasonal TIV or LAIV does not elicit any measurable level of cross-reactive antibody to the novel virus. Results among adults suggest that some degree of preexisting immunity to the novel H1N1 strains exists, especially among adults aged >60 years. One possible explanation is that some adults in this age group have had previous exposure, either through infection or vaccination, to an influenza A (H1N1) virus that is genetically and antigenically more closely related to the novel influenza A (H1N1) virus than are contemporary seasonal H1N1 strains. Ongoing assessment of the cross-reactive antibody

response among persons in different age groups might identify a particular age group that would allow further clarification of the cross-reactive serologic response. Development of a strain-specific vaccine against the novel influenza A (H1N1) virus is needed for optimal protection against the virus among persons of all ages.”

The full article can be found at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5819a1.htm>  
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