

16 February 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 #99

1. AMERICAN JOURNAL OF PATHOLOGY; DOUBLE TROUBLE: BACTERIAL SUPER-INFECTION

AFTER THE FLU: "To explore the mechanisms governing the increased pathogenesis of flu upon super-infection, a group led by Dr. Sally R. Sarawar of the Torrey Pines Institute for Molecular Studies, San Diego, California confirmed that otherwise nonlethal influenza and H. influenzae infections cause high mortality rates in mice when flu infection precedes H. influenzae infection."

2. POST-EXPOSURE PROPHYLAXIS DURING PANDEMIC OUTBREAKS: "Our findings suggest that, in the presence of transmissible drug resistance, strategies that prioritize the treatment of only ill individuals, rather than the prophylaxis of those suspected of being exposed, are most effective in reducing the morbidity and mortality of the pandemic."

3. INTRAMUSCULAR MATRIX-M-ADJUVANTED VIROSOMAL H5N1 VACCINE INDUCES HIGH FREQUENCIES OF MULTIFUNCTIONAL TH1 CD4(+) CELLS AND STRONG ANTIBODY

RESPONSES IN MICE: "Our results highlight that Matrix-M adjuvant is a promising parenteral adjuvant for formulating pandemic candidate vaccines."

4. MASK USE, HAND HYGIENE, AND SEASONAL INFLUENZA-LIKE ILLNESS AMONG YOUNG ADULTS: A RANDOMIZED INTERVENTION TRIAL:

"Neither face mask use and hand hygiene nor face mask use alone was associated with a significant reduction in the rate of ILI cumulatively. These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A(H1N1) pandemic." **[ANALYST NOTE: This article may have relevance at troop training establishments, especially those conducting Basic Training.]**

5. GENERATION OF FULLY HUMAN MONOCLONAL ANTIBODIES NEUTRALIZING INFLUENZA VIRUS - USE OF SPYMEG AS A NOVEL HUMAN LYMPHOCYTE FUSION PARTNER:

"Medical & Biological Laboratories Co., Ltd. (MBL), with the collaboration of Osaka University, has successfully generated several fully human monoclonal antibodies against pandemic A (H1N1 and H3N2) type influenza virus by utilizing blood samples from volunteers who were inoculated with influenza vaccine."

6. MUCOSAL IMMUNITY INDUCED BY ADENOVIRUS-BASED H5N1 HPAI VACCINE CONFERS PROTECTION AGAINST A LETHAL H5N2 AVIAN INFLUENZA VIRUS CHALLENGE:

"That the strategies used to induce multi-antigen-targeted mucosal immunity, such as IN/IM delivery of rAdv-A1, may be a promising approach for developing broad protective vaccines that may be more effective against the new HPAI pandemic strains."

7. SAFETY AND IMMUNOGENICITY OF 2009 PANDEMIC INFLUENZA A H1N1 VACCINES IN CHINA: A MULTICENTRE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED TRIAL:

"The study assessed eight formulations: split-virion formulation containing 7.5 mu g, 15 mu g, or 30 mu g haemagglutinin per dose, with or without aluminium hydroxide adjuvant, and whole-virion formulation containing 5 mu g or 10 mu g haemagglutinin per dose, with adjuvant."

8. HEMAGGLUTININ-PSEUDOTYPED GREEN FLUORESCENT PROTEIN-EXPRESSING INFLUENZA VIRUSES FOR THE DETECTION OF INFLUENZA VIRUS NEUTRALIZING

ANTIBODIES: "These GFP-expressing influenza viruses replicate to high titers in HA-expressing cell lines, but in non-HA-expressing cells, their replication is restricted to a single cycle."

CB Daily Report

AMERICAN JOURNAL OF PATHOLOGY; DOUBLE TROUBLE: BACTERIAL SUPER-INFECTION AFTER THE FLU

NewsRx Health & Science
February 14, 2010

“A common complication of flu infection is a secondary "super-infection" by bacteria, which greatly increases the morbidity and mortality of the disease. The most common bacterial agents found following flu pandemics have been *Streptococcus pneumoniae*, *Haemophilus influenzae*, Group A *Streptococcus*, and *Staphylococcus aureus*. Furthermore, reports of infection with antibiotic-resistant strains have been increasing in recent years.

To explore the mechanisms governing the increased pathogenesis of flu upon super-infection, a group led by Dr. Sally R. Sarawar of the Torrey Pines Institute for Molecular Studies, San Diego, California confirmed that otherwise nonlethal influenza and *H. influenzae* infections cause high mortality rates in mice when flu infection precedes *H. influenzae* infection. Their data confirm a restricted time period for this heightened susceptibility and highlight that excessive bacterial, and not viral, growth is associated with increased lethality. The fact that this increased mortality was observed in both immunocompromised and immunocompetent mice suggests that even normal healthy people are at increased risk for complications following bacterial super-infection.

Lee et al suggest that the "lethal synergy between influenza virus and the bacterial respiratory pathogen, *H. influenzae*, is mediated by innate immunity. They observed that severe damage to the airways was an early event in the co-infected mice, eventually leading to death. This underscores the need for early antiviral and antibiotic treatment to combat severe disease in human patients and highlights the importance of vaccination and effective hygiene measures to prevent secondary bacterial infections during influenza infection. This new model will be useful for further investigating the mechanisms underlying severe disease caused by the interaction between influenza virus and bacteria, which may have resulted in numerous deaths during influenza pandemics and continues to constitute a significant clinical problem in susceptible individuals." Currently ongoing studies suggest that this model may also be useful for identifying target molecules for the development of novel therapeutic agents and strategies.”

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POST-EXPOSURE PROPHYLAXIS DURING PANDEMIC OUTBREAKS

Virus Weekly
February 9, 2010

“The recent emergence of oseltamivir-resistant in treated H1N1 patients has raised concerns about the prudent use of neuraminidase inhibitors for both treatment of ill individuals and post-exposure prophylaxis of close contacts.”

"We extended an established population dynamical model of pandemic influenza with treatment to include post-exposure prophylaxis of close contacts. Using parameter estimates published in the literature, we simulated the model to evaluate the combined effect of treatment and prophylaxis in minimizing morbidity and mortality of pandemic infections in the context of transmissible drug resistance. We demonstrated that, when transmissible resistant strains are present, post-exposure prophylaxis can promote the spread of resistance, especially when combined with aggressive treatment. For a given treatment level, there is an optimal coverage of prophylaxis that minimizes the total number of infections (final size) and this coverage decreases as a higher proportion of infected

individuals are treated. We found that, when treatment is maintained at intermediate levels, limited post-exposure prophylaxis provides an optimal strategy for reducing the final size of the pandemic while minimizing the total number of deaths. We tested our results by performing a sensitivity analysis over a range of key model parameters and observed that the incidence of infection depends strongly on the transmission fitness of resistant strains. Our findings suggest that, in the presence of transmissible drug resistance, strategies that prioritize the treatment of only ill individuals, rather than the prophylaxis of those suspected of being exposed, are most effective in reducing the morbidity and mortality of the pandemic."

The full article can be found at: (S.M. Moghadas, et. al., "Post-exposure prophylaxis during pandemic outbreaks". BMC Medicine, 2009;7():73).

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INTRAMUSCULAR MATRIX-M-ADJUVANTED VIROSOMAL H5N1 VACCINE INDUCES HIGH FREQUENCIES OF MULTIFUNCTIONAL TH1 CD4(+) CELLS AND STRONG ANTIBODY RESPONSES IN MICE

Health Risk Factor Week

February 9, 2010

"Ideally, a candidate pandemic influenza vaccine should elicit rapid and strong cell-mediated and humoral immune responses, which are long-lasting and exhibit broad cross-reactivity against drifted strains. The present study investigated the detailed humoral and cellular immune responses in mice vaccinated intranasally or intramuscularly with inactivated influenza H5N1 (NIBRG-14) virosomal vaccine alone or formulated with Matrix-M adjuvant."

"The intramuscular Matrix-M-adjuvanted vaccine induced a strong immediate and long-term humoral immune response with high cross-reactivity against drifted H5N1 viruses and showed a close-sparing potential. Additionally, the vaccine induced a balanced Th1/Th2 cytokine profile and most importantly high frequencies of multifunctional Th1 CD4(+) cells."

Our results highlight that Matrix-M adjuvant is a promising parenteral adjuvant for formulating pandemic candidate vaccines."

The full article can be found at: (A.S. Madhun, et. al., "Intramuscular Matrix-M-adjuvanted virosomal H5N1 vaccine induces high frequencies of multifunctional Th1 CD4(+) cells and strong antibody responses in mice". Vaccine, 2009;27(52):7367-7376). Link not available.

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MASK USE, HAND HYGIENE, AND SEASONAL INFLUENZA-LIKE ILLNESS AMONG YOUNG ADULTS: A RANDOMIZED INTERVENTION TRIAL

Drug Week

February 12, 2010

"During the influenza A(H1N1) pandemic, antiviral prescribing was limited, vaccines were not available early, and the effectiveness of non-pharmaceutical interventions (NPIs) was uncertain. Our study examined whether use of face masks and hand hygiene reduced the incidence of influenza-like illness (ILI)".

A randomized intervention trial involving 1437 young adults living in university residence halls during the 2006-2007 influenza season was designed. Residence halls were randomly assigned to 1 of 3 groups-face mask use, face masks with hand hygiene, or control-for 6 weeks. Generalized models estimated rate ratios for clinically diagnosed or survey-reported ILI weekly and cumulatively. We observed significant reductions in ILI during weeks 4-6 in the mask and hand hygiene group, compared with the control group, ranging from 35% (confidence interval [CI], 9%-53%) to 51% (CI, 13%-73%), after adjusting for vaccination and other covariates. Face mask use alone showed a similar reduction in

ILI compared with the control group, but adjusted estimates were not statistically significant. Neither face mask use and hand hygiene nor face mask use alone was associated with a significant reduction in the rate of ILI cumulatively. These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A(H1N1) pandemic.”

The full article may be found at: (Allison E. Aiello, et. al., “Mask use, hand hygiene, and seasonal influenza-like illness among young adults: a randomized intervention trial”. Journal of Infectious Diseases, 2010;201(4):491-8). Link not available.

ANALYST NOTE: This article may have relevance at troop training establishments, especially those conducting Basic Training.

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GENERATION OF FULLY HUMAN MONOCLONAL ANTIBODIES NEUTRALIZING INFLUENZA VIRUS - USE OF SPYMEG AS A NOVEL HUMAN LYMPHOCYTE FUSION PARTNER

Immunotherapy Weekly
February 10, 2010

“Medical & Biological Laboratories Co., Ltd. (MBL), with the collaboration of Osaka University, has successfully generated several fully human monoclonal antibodies against pandemic A (H1N1 and H3N2) type influenza virus by utilizing blood samples from volunteers who were inoculated with influenza.

Professor Kazuyoshi Ikuta, Ph. D., at the Department of Virology, Research Institute for Microbial Diseases, Osaka University, has confirmed through in vitro experiments that the fully generated human antibodies can neutralize H3N2 influenza virus strains. Professor Ikuta is now evaluating the preventative and therapeutic effects in an infected mouse model. After completing in vivo experiments in infected animal models with the neutralizing antibodies, MBL plans to commence a collaborative clinical development program with a pharmaceutical company. These neutralizing human IgG antibodies against the influenza virus are expected to be effective in severe infections. In combination with anti-viral drugs these antibodies will have greater success than anti-viral drugs alone.

The therapeutic antibodies were generated by using a special cell line, called SPYMEG. This novel cell line is a human lymphocyte fusion partner, it was co-developed by associate professor Naomasa Yamamoto, Ph. D., of Ohu University and MBL. SPYMEG is the cell line established by the cell fusion of MEG-01 with a murine myeloma cell line. Hybridoma cells of human origin are known to be prone to chromosome deletions. The SPYMEG cell line overcomes that problem, resulting in a higher reliability of cell fusion. Utilization of SPYMEG is a simpler and easier way to generate therapeutic monoclonal antibodies than chimerization, or humanization of mouse monoclonal antibodies generated from immunized mice.”

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MUCOSAL IMMUNITY INDUCED BY ADENOVIRUS-BASED H5N1 HPAI VACCINE CONFERS PROTECTION AGAINST A LETHAL H5N2 AVIAN INFLUENZA VIRUS CHALLENGE

Gene Therapy Weekly
February 11, 2010

"Considering the difficulty in predicting HPAI H5N1 pandemic strains, one strategy used in their design includes the development of formulations with the capacity of eliciting broad cross-protective immunity against multiple viral antigens. To this end we constructed a replication-defective recombinant adenovirus-based avian influenza virus vaccine (rAdv-AI) expressing the codon-optimized M2eX-HA-hCD40L and the M1-M2 fusion genes from HPAI H5N1 human isolate. Although there were no significant

differences in the systemic immune responses observed between the intramuscular prime-intramuscular boost regimen (IM/IM) and the intranasal prime-intramuscular boost regimen (IN/IM), IN/IM induced more potent CD8(+) T cell and antibody responses at mucosal sites than the IM/IM vaccination, resulting in more effective protection against lethal H5N2 avian influenza (AI) virus challenge."

"That the strategies used to induce multi-antigen-targeted mucosal immunity, such as IN/IM delivery of rAdv-AI, may be a promising approach for developing broad protective vaccines that may be more effective against the new HPAI pandemic strains."

The full article can be found at: (K.S. Park, et. al., "Mucosal immunity induced by adenovirus-based H5N1 HPAI vaccine confers protection against a lethal H5N2 avian influenza virus challenge". *Virology*, 2009;395(2):182-189). Link not available.

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SAFETY AND IMMUNOGENICITY OF 2009 PANDEMIC INFLUENZA A H1N1 VACCINES IN CHINA: A MULTICENTRE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED TRIAL

Preventive Medicine Week

February 7, 2010

"We assessed the safety and immunogenicity of eight formulations of 2009 pandemic influenza A H1N1 vaccine produced by ten Chinese manufacturers," scientists in Beijing, People's Republic of China report.

In this multicentre, double-blind, randomised trial, 12 691 people aged 3 years or older were recruited in ten centres in China. In each Centre, participants were stratified by age and randomly assigned by a random number table to receive one of several vaccine formulations or placebo. The study assessed eight formulations: split-virion formulation containing 7.5 mu g, 15 mu g, or 30 mu g haemagglutinin per dose, with or without aluminium hydroxide adjuvant, and whole-virion formulation containing 5 mu g or 10 mu g haemagglutinin per dose, with adjuvant. All formulations were produced from the reassortant strain X-179A (A/California/07/2009-A/PR/8/34). We analysed the safety (adverse events), immunogenicity (geometric mean titre [GMT] of haemagglutination inhibition antibody), and seroprotection (GMT \geq 1:40) of the formulations. Analysis was by per protocol. Two sites registered their trial with ClinicalTrials.gov, numbers NCT00956111 and NCT00975572. The other eight studies were registered with the State Food and Drug Administration of China. 12691 participants received the first dose on day 0, and 12348 participants received the second dose on day 21. The seroprotection rate 21 days after the first dose of vaccine ranged from 69.5% (95% CI 65.9-72.8) for the 7.5 mu g adjuvant split-virion formulation to 92.8% (91.9-93.6) for the 30 mu g non-adjuvant split-virion formulation. The seroprotection rate was 86.5% (796 of 920; 84.1-88.7) in recipients of one dose of the 7.5 mu g non-adjuvant split-virion vaccine compared with 9.8% (140 of 1432; 8.3-11.4) in recipients of placebo ($p < 0.0001$). One dose of the 7.5 mu g non-adjuvant split-virion vaccine induced seroprotection in 178 of 232 children (aged 3 years to <12 years; 76.7%, 70.7-82.0), 211 of 218 adolescents (12 years to <18 years; 96.8%, 93.5-98.7), 289 of 323 adults (18-60 years; 89.5%, 85.6-92.6), and 118 of 147 adults older than 60 years (80.3%, 72.9-86.4), meeting the European Union's licensure criteria for seroprotection in all age-groups. In children, a second dose of the 7.5 mu g formulation increased the seroprotection rate to 97.7% (215 of 220, 94.8-99.3). Adverse reactions were mostly mild or moderate, and self-limited. Severe adverse effects occurred in 69 (0.6%, 0.5-0.8) recipients of vaccine compared with one recipient (0.1%, 0-0.2) of placebo. The most common severe adverse reaction was fever, which occurred in 25 (0.22%; 0.14-0.33) recipients of vaccine after the first dose and four (0.04%; 0.01-0.09) recipients of vaccine after the second dose compared with no recipients of placebo after either dose."

"One dose of non-adjuvant split-virion vaccine containing 7.5."

The full article can be found at: (X.F. Liang, et. al., "Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial". *Lancet*, UNKNOWN DATE;375(9708):56-66). Link not available.

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HEMAGGLUTININ-PSEUDOTYPED GREEN FLUORESCENT PROTEIN-EXPRESSING INFLUENZA VIRUSES FOR THE DETECTION OF INFLUENZA VIRUS NEUTRALIZING ANTIBODIES

Drug Week

February 12, 2010

"Detection of NABs in serum samples is critical to evaluate the prevalence and spread of new virus strains. Here we describe the development of a simple, sensitive, specific, and safe screening assay for the rapid detection of NABs against highly pathogenic influenza viruses under biosafety level 2 (BSL-2) conditions. This assay is based on the use of influenza viruses in which the hemagglutinin (HA) gene is replaced by a gene expressing green fluorescent protein (GFP)."

"These GFP-expressing influenza viruses replicate to high titers in HA-expressing cell lines, but in non-HA-expressing cells, their replication is restricted to a single cycle."

The full article can be found at: (L. Martinez-Sobrido, et. al., "Hemagglutinin-pseudotyped green fluorescent protein-expressing influenza viruses for the detection of influenza virus neutralizing antibodies". *Journal of Virology*, 2010;84(4):2157-63). Link not available.

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