4 May 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 #110

1. INTRODUCTION OF VIRULENCE MARKERS IN PB2 OF PANDEMIC SWINE-ORIGIN INFLUENZA VIRUS DOES NOT RESULT IN ENHANCED VIRULENCE OR TRANSMISSION: *"We conclude that surveillance studies aimed at detecting S-OIVs with increased virulence or transmission should not rely solely on virulence markers identified in the past but should include detailed characterization of virus phenotypes, guided by genetic signatures of viruses detected in severe cases of disease in humans."*

2. IDENTIFICATION OF INFLUENZA A PANDEMIC (H1N1) 2009 VARIANTS DURING THE FIRST 2009 INFLUENZA OUTBREAK IN MEXICO CITY: *"The sequencing of partial fragments of the HA and NA genes did not show the presence of previously described mutations affecting known sites of antiviral resistance in seasonal influenza A such as the H275Y (oseltamivir resistance), R293 or N295 etc."*

3. LICENSURE OF A HIGH-DOSE INACTIVATED INFLUENZA VACCINE FOR PERSONS AGED ≥65 YEARS (FLUZONE HIGH-DOSE) AND GUIDANCE FOR USE --- UNITED STATES, 2010: *"Persons aged ≥65 years are at greater risk for hospitalization and death from seasonal influenza compared with other age groups (1,2), and they respond to vaccination with lower antibody titers to influenza hemagglutinin (an established correlate of protection against influenza) compared with younger adults (3). On December 23, 2009, the Food and Drug Administration (FDA) licensed an injectable inactivated trivalent influenza vaccine (Fluzone High-Dose, Sanofi-Pasteur) that contains an increased amount of influenza virus hemagglutinin antigen compared with other inactivated influenza vaccines such as Fluzone. Fluzone High-Dose is licensed as a single dose for use among persons aged ≥65 years and will be available beginning with the 2010--11 influenza season."*

4. [AU] AN AUDIT OF PANDEMIC (H1N1) 2009 INFLUENZA VACCINE WASTAGE IN GENERAL PRACTICE: *"These results provide evidence that multidose vials (discarded within 24 hours of first use) are an inefficient method of presenting pandemic influenza vaccines for general practice use. Wastage was substantial. This study is limited to the program's first month, so initial results may not reflect results over the whole program. However, if similar wastage occurred nationally, over 7.5 million of the 19 million doses available to Australians could be wasted. Nevertheless, the low unit cost and rapid*

production advantages of multidose vials may justify their use when faced with an urgent threat, and if used in mass vaccination clinics."

5. COST-EFFECTIVENESS OF PNEUMOCOCCAL POLYSACCHARIDE VACCINE AMONG HEALTHCARE WORKERS DURING AN INFLUENZA PANDEMIC: *"Vaccinating all healthcare workers to protect against pneumococcal disease during a pandemic influenza outbreak is likely to be economically reasonable from the societal standpoint….. However, PPV is expensive from the hospital perspective, which might prevent implementation of a PPV program unless it is externally subsidized."*

6. DETERMINATION OF SERUM ANTIBODIES AGAINST SWINE-ORIGIN INFLUENZA A VIRUS H1N1/09 BY IMMUNOFLUORESCENCE, HAEMAGGLUTINATION INHIBITION, AND BY NEUTRALIZATION TESTS: HOW IS THE PREVALENCE RATE OF PROTECTING ANTIBODIES IN HUMANS?: *"Expecting the next waves of influenza A/H1N1v infections, HI testing may avoid vaccinations under special risk of severe or hidden adverse reactions."*

CB Daily Report

Chem-Bio News

INTRODUCTION OF VIRULENCE MARKERS IN PB2 OF PANDEMIC SWINE-ORIGIN INFLUENZA VIRUS DOES NOT RESULT IN ENHANCED VIRULENCE OR TRANSMISSION
Genomics & Genetics Weekly
April 30, 2010

""Mutations E627K and D701N in the PB2 protein have previously been identified as determinants of avian and pandemic influenza virus virulence in mammals. These mutations were absent in S-OIVs detected early in the 2009 pandemic. Here, using reverse genetics, mutations E627K, D701N, and E677G were introduced into the prototype S-OIV A/Netherlands/602/2009, and their effects on virus replication, virulence, and transmission were investigated. Mutations E627K and D701N caused increased reporter gene expression driven by the S-OIV polymerase complex. None of the three mutations affected virus replication in vitro. The mutations had no major impact on virus replication in the respiratory tracts of mice and ferrets or on pathogenesis. All three mutant viruses were transmitted via aerosols or respiratory droplets in ferrets. Thus, the impact of key known virulence markers in PB2 in the context of current S-OIVs was surprisingly small. This study does not exclude the possibility of emergence of S-OIVs with other virulence-associated mutations in the future."

"We conclude that surveillance studies aimed at detecting S-OIVs with increased virulence or transmission should not rely solely on virulence markers identified in the past but should include detailed characterization of virus phenotypes, guided by genetic signatures of viruses detected in severe cases of disease in humans."

The full article can be found at: (S. Herfst, et. al., "Introduction of virulence markers in PB2

of pandemic swine-origin influenza virus does not result in enhanced virulence or transmission". Journal of Virology, 2010;84(8):3752-8). Link not available.

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IDENTIFICATION OF INFLUENZA A PANDEMIC (H1N1) 2009 VARIANTS DURING THE FIRST 2009 INFLUENZA OUTBREAK IN MEXICO CITY
TB & Outbreaks Week
May 4, 2010

"As a consequence the World Health Organisation has declared the first Influenza pandemic of the 21st century. To describe clinically and molecularly the first outbreak of influenza A pH1N1 (2009) during 1-5 May to establish a baseline of epidemiological data for pH1N1. Also, to monitor for the emergence of antiviral resistance, and mutations affecting virulence and transmissibility. Samples were collected from 751 patients with influenza-like symptoms throughout Mexico City and were tested for influenza A pH1N1 (2009) using real-time PCR. In the samples that were positive for influenza A pH1N1 (2009) fragments from the haemagglutinin (H1) and neuraminidase (N1) genes were sequenced. A total of 203/751 (27%) patients were positive for the pandemic H1N1 (2009) virus (53% male and 47% female). The 0-12-year-old group was the most affected 85/751 (42%). Sequence analysis showed five new variants of the pandemic H1N1 (2009) virus for NA: G249E (GQ292900), M269I (GQ292892), Y274H (GQ292913), T332A (GQ292933), N344K (GQ292882), and four variants for HA: N461K (GQ293006), K505R (GQ292989), I435V (GQ292995), I527N (GQ292997). We have provided a baseline of epidemiological data from the first outbreak of influenza A pH1N1 (2009) during 1-5 May in Mexico City."

"The sequencing of partial fragments of the HA and NA genes did not show the presence of previously described mutations affecting known sites of antiviral resistance in seasonal influenza A such as the H275Y (oseltamivir resistance), R293 or N295 etc."

The full article can be found at: (H.M. Zepeda, et. al., "Identification of influenza A pandemic (H1N1) 2009 variants during the first 2009 influenza outbreak in Mexico City". Journal of Clinical Virology, 2010;48(1):36-9). Link not available.

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LICENSURE OF A HIGH-DOSE INACTIVATED INFLUENZA VACCINE FOR PERSONS AGED ≥65 YEARS (FLUZONE HIGH-DOSE) AND GUIDANCE FOR USE --- UNITED STATES, 2010
US Centers for Disease Control and Prevention
April 30, 2010

"Persons aged ≥65 years are at greater risk for hospitalization and death from seasonal influenza compared with other age groups (1,2), and they respond to vaccination with lower antibody titers to influenza hemagglutinin (an established correlate of protection against

influenza) compared with younger adults (3). On December 23, 2009, the Food and Drug Administration (FDA) licensed an injectable inactivated trivalent influenza vaccine (Fluzone High-Dose, Sanofi-Pasteur) that contains an increased amount of influenza virus hemagglutinin antigen compared with other inactivated influenza vaccines such as Fluzone. Fluzone High-Dose is licensed as a single dose for use among persons aged ≥65 years and will be available beginning with the 2010--11 influenza season. The Advisory Committee on Immunization Practices (ACIP) reviewed data from prelicensure clinical trials on the safety and immunogenicity of Fluzone High-Dose and expressed no preference for the new vaccine over other inactivated trivalent influenza vaccines (4). This report summarizes the FDA-approved indications for Fluzone High-Dose and provides guidance from ACIP for its use.

Standard dose inactivated trivalent influenza vaccines contain a total of 45 µg (15 µg of each of the three recommended strains) of influenza virus hemagglutinin antigen per 0.5mL dose (5). In contrast, Fluzone High-Dose is formulated to contain a total of 180 µg (60 µg of each strain) of influenza virus hemagglutinin antigen in each 0.5mL dose. Like other inactivated influenza vaccines, Fluzone High-Dose is administered as an intramuscular injection (6). Fluzone High-Dose is available as a single-dose prefilled syringe formulation and is distinguished from Fluzone by a gray syringe plunger rod. As with other 2010--11 influenza vaccines, Fluzone High-Dose will contain antigens of the three recommended virus strains: A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like (7).

Immunogenicity data from three studies among persons aged ≥65 years indicated that, compared with standard dose Fluzone, preparations of Fluzone High-Dose elicited significantly higher hemagglutination inhibition (HI) titers against all three influenza virus strains that were included in seasonal influenza vaccines recommended during the study period (8--10)……"

Solicited injection site reactions and systemic adverse events were more frequent after vaccination with Fluzone High-Dose compared with standard Fluzone, but typically were mild and transient (8--10). In the largest study, 915 (36%) of 2,572 persons who received Fluzone High-Dose, compared with 306 (24%) of 1,275 persons who received Fluzone, reported injection site pain ≤7 days after vaccine administration. In the same study, significantly more Fluzone High-Dose recipients (1.1%) reported moderate (>100.4°F--≤102.2°F [>38°C--≤39°C]) to severe (>102.2°F [>39°C]) fever, compared with Fluzone recipients (0.3%)(9)."

The full article can be found at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5916a2.htm

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[AU] AN AUDIT OF PANDEMIC (H1N1) 2009 INFLUENZA VACCINE WASTAGE IN GENERAL PRACTICE

By Caroline E Turnour, Stephen J Conaty, Michelle A Cretikos
The Medical Journal of Australia
March 24, 2010

“To the Editor: From 30 September 2009, the Australian Government began offering free pandemic (H1N1) 2009 influenza vaccine (Panvax, CSL Limited, Melbourne, VIC), using either 10-dose (5 mL) or 20-dose (10 mL) vials.1 Multidose vials are not used routinely in Australia, and are designed for high-volume vaccination clinics.2 Once pierced, a Panvax vial must be used within 24 hours or discarded.3 We investigated vaccine wastage in general practice during the first month of the vaccine’s availability.”

…..

“There was significantly less wastage in practices with access to 5 mL vials (median wastage, 30%) than practices that had only 10 mL vials (median wastage, 50%) ($P < 0.001$; Wilcoxon rank-sum test). There was no significant difference in the proportion of doses wasted between the 70 practices that organised vaccination clinics and the 63 practices that did not (median wastage, 43% v 40%; $P = 0.9$; Wilcoxon rank-sum test). There was also no statistically significant difference in the proportion wasted between solo and multidoctor practices (median wastage, 43% v 34%; $P = 0.2$; Wilcoxon rank-sum test) although the absolute wastage level was lower for multidoctor practices.

These results provide evidence that multidose vials (discarded within 24 hours of first use) are an inefficient method of presenting pandemic influenza vaccines for general practice use. Wastage was substantial. This study is limited to the program’s first month, so initial results may not reflect results over the whole program. However, if similar wastage occurred nationally, over 7.5 million of the 19 million doses available to Australians could be wasted. Nevertheless, the low unit cost and rapid production advantages of multidose vials may justify their use when faced with an urgent threat, and if used in mass vaccination clinics.

Wastage could be reduced by increasing the availability of 5 mL multidose vials, but not (according to our data) by organising general practice vaccination clinics. Extending the vaccine shelf-life from 24 hours to 28 days, to align with licence conditions in the United States,4 could decrease wastage, as it may be that the short shelf-life results in more wastage than does supplying the vaccine in multidose vials. No rationale for the shorter shelf-life in Australia has been found, but we surmise it was set as a precaution to reduce the risk of contamination. Doses saved through reduced wastage could be used to increase Australia’s donation of vaccine to developing countries.5”

The full article can be found at: http://www.mja.com.au/public/issues/192_09_030510/letters_030510_fm-1.html

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COST-EFFECTIVENESS OF PNEUMOCOCCAL POLYSACCHARIDE VACCINE AMONG HEALTHCARE WORKERS DURING AN INFLUENZA PANDEMIC
World Disease Weekly
April 20, 2010

“To assess the usefulness and cost-effectiveness of pneumococcal polysaccharide vaccine (PPV) among healthcare workers compared with nonuse of PPV during an influenza pandemic. Markov modeling was used to estimate the cost-effectiveness of PPV in previously unvaccinated healthcare workers during an influenza pandemic."

"Invasive pneumococcal disease (IPD) incidence rates were incorporated into the model, which assumed that IPD events occurred at twice the usual rate during a year of pandemic influenza. Societal and hospital perspectives were examined. Assumptions were that pneumococcal disease transmission from healthcare worker to patient did not occur, heightened IPD risk occurred for only 1 year, and PPV did not prevent noninvasive pneumonia, all of which potentially bias against vaccination. From a societal standpoint, PPV of healthcare workers during an influenza pandemic is economically reasonable, costing $2935 per quality-adjusted life-year gained; results were robust to variation in multiple sensitivity analyses. However, from the hospital perspective, vaccinating healthcare workers was expensive, costing $1676 per employee absence day avoided, given an IPD risk that (although increased) would remain less than 1%. Vaccinating all healthcare workers to protect against pneumococcal disease during a pandemic influenza outbreak is likely to be economically reasonable from the societal standpoint.”

"However, PPV is expensive from the hospital perspective, which might prevent implementation of a PPV program unless it is externally subsidized."

The full article can be found at: (K.J. Smith, et. al., “Cost-effectiveness of pneumococcal polysaccharide vaccine among healthcare workers during an influenza pandemic”. The American Journal of Managed Care, 2010;16(3):200-6). Link not available.

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INFLUENZA A VIRUS H1N1/09 BY IMMUNOFLUORESCENCE, HAEMAGGLUTINATION INHIBITION, AND BY NEUTRALIZATION TESTS: HOW IS THE PREVALENCE RATE OF PROTECTING ANTIBODIES IN HUMANS?
Medical Devices & Surgical Technology Week
May 9, 2010

“"Mainly young people, but less elderly were affected and presented severe and even lethal courses of disease. Since virus-specific antibodies are commonly regarded as markers of partial or complete immunoprotection, we performed antibody determinations in serum samples obtained from people before and after the pandemic has arrived in our region (Frankfurt/M., Germany). The assays were done by indirect immunofluorescence, by neutralization test, and by a haemagglutination inhibition test (HI), which was established in a practical modification for general and easy use. Among 145 individuals, of whom serum specimens had been drawn before the onset of pandemic, 19 revealed humoral immunity, i. e. titres of H1N1v neutralizing antibodies (at least 1:64). Eleven were older than 60 years, one belonged to the age group 40-59 years, three to the age group 20-39 years, and two to the age group 15-19 years. After the onset of pandemic in Frankfurt, serum specimens drawn from n=225 randomly selected patients of our local university hospital were investigated for antibodies against H1N1v by HI, which is generally recommended for

routine check of immunity. Twenty-eight individuals revealed the protecting antibody titer of at least 1:40. The age distribution had moved to mean age groups. The results fit to the incidence of influenza A/H1N1(09) disease, as confirmed by RT-PCR in patients admitted to our hospital, peaking in the younger age groups up to 30 years (second affected group: 30-40 years). While commonly used solid-phase antibody tests (like immunofluorescence) are not suitable to diagnose passed H1N1(09) infection and acquired immunity, this can be easily done by HI."

"Expecting the next waves of influenza A/H1N1v infections, HI testing may avoid vaccinations under special risk of severe or hidden adverse reactions."

The full article can be found at: (R. Allwinn, et. al., "Determination of serum antibodies against swine-origin influenza A virus H1N1/09 by immunofluorescence, haemagglutination inhibition, and by neutralization tests: how is the prevalence rate of protecting antibodies in humans?", Medical Microbiology and Immunology, 2010;199(2):117-21). Link not available.

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