National Collaborating Centre for Infectious Diseases
Centre de collaboration nationale des maladies infectieuses

Purple Paper

Pandemic pH1N1 Weekly Literature Synthesis
(Week of November 15-21, 2009)

Seasonal Influenza Vaccine

Effectiveness of 2008-09 trivalent influenza vaccine against 2009 pandemic influenza (H1N1) – United States, May-June 2009.
CDC. *MMWR 2009; 302:1241-1245.*
Infection and death from influenza A H1N1 virus in Mexico : a retrospective analysis.
Echevarría-Zuno S et al. *Lancet. Published online November 11, 2009.*

Two studies were published last week that examined the effectiveness of seasonal influenza vaccine against pH1N1.

In the **case-base study** conducted in **the USA**, investigators compared seasonal influenza vaccination coverage of persons aged > 18 years with laboratory-confirmed pH1N1 illness during May-June 2009 with an estimate of vaccination coverage in the *base* population. Data were gathered from CDC surveillance reports from eight states for 356 confirmed cases and from the Behavioral Risk Factor Surveillance Survey (BRFSS) for 20,689 controls from the base populations of these states. After adjusting for confounding by underlying medical conditions in the patient and base vaccination coverage estimates, the age group-specific point estimates for vaccine effectiveness did not indicate a protective or harmful effect of the seasonal influenza vaccine toward pH1N1. The same was true for the overall vaccine effectiveness estimate after adjusting for both age and underlying medical conditions in the patient and base vaccination coverage estimates.

In the **case-control study** conducted in **Mexico**, the authors explored the possible association between 2008/09 seasonal influenza vaccination and development of pH1N1 illness. Data were gathered and analyzed for laboratory-confirmed positive (n=6,945) and negative (n=10,294) cases with influenza-like illness who attended clinics of the Mexican Institute for Social Security network during the surveillance period of April 28-July 31, 2009. Results suggested that people who had received the 2008/09 seasonal influenza vaccine had a reduced risk of pH1N1; however, possible confounding by underlying chronic conditions was not addressed during data analysis.

NCCID Comments:
There are limitations in both studies. For example, the dependence on self-reporting of vaccination status and differences in health-seeking behaviour between patient and control groups could have introduced bias. Nevertheless, taken together, these results suggest that seasonal influenza vaccination has little or no protective or harmful effect toward pH1N1. These findings are consistent with other studies that also investigated this issue:

1. A case-control study in Australia based on data from sentinel influenza surveillance showed no evidence of protection against pH1N1 from seasonal influenza vaccination. The overall age-adjusted vaccine effectiveness was 3% for all patients [1].
2. An investigation of a cluster of 87 reported cases of pH1N1 at a private school in Nova Scotia indicated similar pH1N1 attack rates in two groups of students whose seasonal influenza vaccine uptake was 100% and 15% [2].
3. A hospital-based case-control study in Mexico reported a vaccine effectiveness of 73% in the 2008/09 seasonal influenza vaccine against pH1N1. However, as the authors noted, controls had a higher prevalence of underlying chronic conditions compared to the general population, thus possibly leading to higher vaccination coverage and skewing vaccine effectiveness toward the positive [3].

Efficacy of a single dose of live attenuated influenza vaccine in previously unvaccinated children: a post hoc analysis of three studies of children aged 2 to 6 years.
Block SL et al. *Clin Ther 2009; 31:2140-2147.*

In **the USA**, CDC recommends that children aged < 9 years who have previously not been vaccinated against influenza receive 2 doses of either

inactivated or live attenuated seasonal influenza vaccine (LAIV). Because the regimented two doses are often not adhered to, the question regarding the efficacy of a single dose in previously unvaccinated children needs to be addressed. Three independent studies had been published that investigated the efficacy and safety of one vs. two doses of LAIV in previously unvaccinated children between the ages 6 months and 7 years. This paper presents reanalysis of data from these three studies to focus on a subgroup of children aged 2-6 years.

The three parent studies were all randomized, double-blind, placebo-controlled clinical trials conducted during two consecutive influenza seasons that enrolled only healthy children without any underlying medical conditions. Children who had no previous LAIV were randomly assigned in the first year to receive either one or two doses of LAIV. In the second year, all children received a single LAIV dose. Of the three studies, two compared the efficacy of 1 vs. 2 doses of LAIV in the same season. The primary efficacy end point in both years for all studies was the incidence of the first episode of laboratory-confirmed influenza illness caused by a virus subtype antigenically similar to that in the vaccine. A subgroup of children aged 2-6 years at the time of vaccination was identified and used for reanalysis. All new statistical analyses were based on the original population and analytical methods of the parent studies from which data were drawn.

Results of this reanalysis showed that one dose of LAIV was slightly less effective than two doses in the same season, but the difference was not statistically significant. In fact, one dose of LAIV appeared to provide approximately 90% of the protection of 2 doses and suggested that a single dose was effective in preventing influenza in previously unvaccinated children between the ages 2 and 6 years. When vaccine efficacy was measured again in both one- and two-dose groups after all children were revaccinated with a single dose in the following year, efficacy appeared to be similar in the two groups. The most common adverse effects associated with the first LAIV dose among children of this age group were runny nose/nasal congestion, cough, myalgia and low-grade fever. In general, these events decreased after the second dose, except for cough.

NCCID Comments:
It should be noted that the findings of this study are **not applicable** in the Canadian setting since seasonal influenza vaccine is only available in the inactivated, split virion format in Canada. Unlike the inactivated seasonal influenza vaccine, LAIV contains a weakened but live virus which can infect the respiratory lining when given intranasally. By mimicking natural infection but limiting the extent to which the vaccine virus can replicate, LAIV can induce a stronger immunity than the inactivated vaccine without causing systemic influenza symptoms. Consequently, this may explain the one-dose efficacy of LAIV.

The National Advisory Committee on Immunization recommends that children between the age of 6 months and 9 years should receive two doses of the inactivated seasonal influenza vaccine if they have never been previously vaccinated. Once they have received their first 2-dose regimen, a single dose will suffice in following years. The first 2-dose regimen in children with no prior influenza vaccination is necessary to establish adequate immunity against seasonal influenza. In fact, several studies have shown that a single dose of the inactivated vaccine in children aged <5 years provides little or no protection [4-7].

Clinically Ill Children with H1N1

Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza.

O'Riordan S et al. *CMAJ. Published online November 19, 2009.*

To compare the risk factors and outcomes of hospitalized children ill with 2009 pH1N1 to those with seasonal influenza during the previous five influenza seasons (2004/05-2008/09), investigators from the Hospital for Sick Children, **Toronto, Ontario**, used a **retrospective case-control study design** to analyze data extracted from hospital charts. A total of 58 laboratory-confirmed pH1N1 cases and 200 laboratory-confirmed seasonal influenza cases were included in this study. Since there were no significant differences in

demographic characteristics and risk factors or outcomes between seasonal influenza patients across the five seasons, data for these patients were aggregated and treated as one study group.

The children admitted with pH1N1 were significantly older than their seasonal counterparts, with a larger proportion over the age of 5 years. The most common symptoms among pH1N1 patients were fever and cough – in accord with the clinical features of adults and children clinically ill with pH1N1 examined in other studies. There were no differences between children with pH1N1 and seasonal influenza in the duration of hospital stay, the need for intensive care or mechanical ventilation, indicating that the severity of disease in children caused by pH1N1 and seasonal influenza were similar.

Asthma was the most prevalent risk factor among children with pH1N1 and seasonal influenza. Although children with pH1N1 were significantly more likely to have asthma than children with seasonal influenza, there was no apparent difference in the spectrum of asthma severity between the two groups. This suggests that even children with mild asthma are at risk of pH1N1-related complications. Obesity was also a probable risk factor for pH1N1 illness in this study group.

H1N1 Outbreak in Schools

Pandemic (H1N1) 2009 virus outbreak in a school in London, April-May 2009: an observational study.
Calatayud L et al. *Epidemiol Infect. Published online November 20, 2009.*
Notes from the field: outbreak of 2009 pandemic influenza A (H1N1) virus at a large public university in Delaware, April-May 2009.
Iuliano AD et al. *Clin Infect Dis. Published online November 13, 2009.*

Two studies published last week examined the transmission dynamics of pH1N1 in the school setting during the first wave of the pandemic.

In the first study, the chain of transmission of pH1N1 was traced in a cluster of 91 symptomatic cases in a school in London, UK. Although implementation of mass anti-viral prophylaxis and school closure might have dampened the spread of pH1N1 within the index school, the virus continued to spread outside to two other schools through household contacts.

In the second study, a cross-sectional survey was conducted among students, faculty and staff at the University of Delaware to examine factors associated with transmission.

Although the school format and age of the student body were considerably different between the two settings, two common features associated with the two school outbreaks have emerged. First, having travelled to a risk area was significantly associated with pH1N1 in the early phase of the first wave. In fact, the two index cases of the London school outbreak had travelled to a risk area within 7 days of symptoms onset. Second, large social gatherings outside of school appeared to have facilitated the spread of pH1N1 among students.

Economic Benefits of Mitigation Strategies

The economic-wide impact of pandemic influenza on the UK: a computable general equilibrium modelling experiment.
Smith RD et al. *BMJ 2009; 339:b4571.*
Economic value of seasonal and pandemic influenza vaccination during pregnancy.
Beigi RH et al. *Clin Infect Dis. Published online November 13, 2009.*

Two simulation modelling studies published last week examined the economic value associated with various mitigation strategies during pandemic periods.

In the first model, which was based on the 2004 UK economy, the potential economic impact of pandemic influenza, school closures and vaccination was estimated as the % loss of gross domestic product (GDP). Scenarios were simulated for low, medium or high influenza attack rates, and low, high or extreme case-fatality rates. An interesting aspect of this model is the consideration of how prophylactic absenteeism – absence from work due to fear of infection – also impacts the economy during high or extreme pandemic scenarios.

In all scenarios, school closure causes the greatest % GDP loss even when no mitigations are implemented. The difference in % GDP loss between school closure and no mitigation is the most pronounced when case fatality rate is low. Compared to no mitigation, vaccination could result in large relative savings for both low and high fatality scenarios. In the most extreme pandemic scenario, a vaccine that has 80% efficacy, even if it requires two doses, could keep the loss in GDP to below the level equivalent to little over half the impact of the 2009 recession experienced in the UK. A good vaccine could also avert the transition point that triggers prophylactic absenteeism in a high fatality pandemic.

The second study primarily focused on the economic benefits of maternal vaccination strategies during seasonal and pandemic influenza periods. Simulations were conducted from both societal and third-party payer perspectives for single- and two-dose strategies. Results show that maternal influenza vaccination is cost-effective at disease prevalence and severity rates consistent with seasonal influenza epidemics regardless of whether a single- or two-dose strategy is adopted. Furthermore, as influenza prevalence and severity escalates to the level of a pandemic, cost-effectiveness of vaccination also increases.

NCCID Comments:
Vaccination is one of the major pillars of public health in infection control and prevention. In addition to the unequivocal benefits to health, it is one of the most cost-effective interventions in the public health arsenal. These studies, along with the simulation study that investigated the effectiveness of vaccination in reducing influenza attack rates (see first issue of *Purple Paper*), suggest that vaccination continues to be the most important mitigation strategy – both in terms of health benefits and economic impact – in curtailing the spread of pH1N1.

Pre-Existing Immunity to H1N1

Pre-existing immunity against swine-origin H1N1 influenza viruses in the general human population.
Greenbaum JA et al. *Proc Natl Acad Sci USA. Published online November 16, 2009.*

Immunity has both non-specific and specific components. Whereas innate, or non-specific, immunity consists of basic resistance elements against invading pathogens; acquired, or specific, immunity is comprised of armies of specialized cells and their products. When a pathogen invades the body, innate defense mechanisms provide the first line of host defense. If the invading organism eludes the non-specific innate defense mechanisms, an acquired immune response is then enlisted. Acquired immunity does not operate in isolation; rather, it supplements and augments the innate defense mechanism so that a more effective pathogen-specific response can be launched to fight the infection. A very important feature of the acquired immunity is its ability to "remember" past invading organisms. After an infection is cleared, immunological memory is established so that when the same pathogen invades the body again, a much more rapid response will be elicited.

There are two arms within acquired immunity: humoral (or antibody) immunity and cellular immunity. The primary goal of humoral immunity is to stimulate B cells to produce antibodies that can neutralize an invading organism before infection can take place. Vaccines work primarily within the humoral immunity branch by mimicking natural infection to "trick" the body into producing antibodies and establishing immunological memory. When the real pathogen invades at a later time, the body will be equipped to fight the invading organism quickly.

When a virus infects a cell, the virus turns the cell into its own factory to replicate itself. One important function of cellular immunity is to stimulate T cells to destroy cells that have been taken over by viruses in order to control and clear the infection. The stronger the T cell response, the less severe the disease.

Both B and T cells recognize invading pathogens by detecting specific features of the organism called epitopes. An epitope is essentially a short stretch of amino acids derived from the organism's proteins. Hence, each organism can have many different epitopes that many different B and T cells can recognize. Once the organism is recognized, development of the appropriate specific immune response will ensue. (Note: B cells make antibodies

against the same epitopes they recognize. Therefore, only a B cell that recognizes an epitope on a surface protein of the invading organism can produce a neutralizing antibody.)

When the novel pH1N1 emerged, a major concern was that the virus may be so different from seasonal H1N1 that little protective immunity existed in the human population. The authors addressed the issue of pre-existing immunity by examining whether there are epitopes in pH1N1 that are shared among other seasonal H1N1 strains (1988-2008) and can be targeted by memory B and T cells against seasonal H1N1 influenza. These are the findings of this study:

1. The authors found eight B cell epitopes and 111 T cell epitopes in pH1N1 that are shared among other seasonal H1N1 strains.
2. Of the eight B cell epitopes identified in pH1N1, only one is found in the hemagglutinin (HA) protein, suggesting that this epitope is also the only possible target for neutralizing antibodies.
3. Experiments were performed to examine whether memory T cells would respond to epitopes identified in pH1N1 in comparison to those identified in the 2008 seasonal H1N1 strain. It was found the T cell response to epitopes from the 2008 seasonal H1N1 influenza strain was slightly higher than those from pH1N1; however, the difference was not statistically significant.

The findings of this study suggest that a degree of pre-existing immunity against pH1N1 is present in the human population. This pre-existing immunity is the result of cross-reactive immune responses to common elements shared between prior seasonal H1N1 influenza strains and pH1N1. While little cross-reactive B cell immunity against pH1N1 exists, a more substantial cross-reactive T cell immunity is present in people who were previously infected by seasonal influenza. This is in agreement with the observation that although a majority of the general population is susceptible to pH1N1 (i.e., attack rates are high), the severity of the disease remains mild.

Echinacea and pH1N1

Anti-viral properties and mode of action of standardized *Echinacea purpurea* extract against highly pathogenic avian influenza virus (H5N1, H7N7) and swine-origin H1N1 (S-OIV).
Pleschka S et al. *Virol J. Published online November 13, 2009.*

Echinacea is a widely available health supplement that is used commonly to prevent and treat cold and influenza symptoms. In this study, the authors investigated the anti-viral properties of one standardized *Echinacea* species extract product (Echinaforce® [EF]) against highly pathogenic avian influenza viruses (H5N1 and H7N7) and pH1N1 by using different laboratory experimental methods. Below is a summary of the findings.

1. EF reduced the cytopathic effects of influenza in a dose-response manner. Both avian influenza viruses and pH1N1 were susceptible to inhibitory effects of EF.
2. EF acted at an early stage in the replication cycle of influenza. Optimal anti-viral effect required direct contact with the viral particles.
3. EF appeared to exert its anti-viral effect through interaction with hemagglutinin – influenza's surface protein responsible for cell entry.
4. When influenza viruses were pre-treated with EF before infection, the overall proportion of infected cells is reduced. However, once the virus entered the cell, replication was not affected.
5. To test whether the influenza virus can develop resistance to EF, the authors grew successive generations of virus in cell cultures containing EF and in parallel cell cultures containing oseltamivir (Tamiflu®) for comparison. No EF-resistant influenza emerged, in contrast to oseltamivir. However, oseltamivir-resistant influenza continued to be susceptible to EF.

NCCID Comments:
Results of this industry-sponsored study suggest that possible anti-viral activity of a commercially available *Echinacea* species extract against influenza, Echinaforce® (EF), is mediated through interaction with hemagglutinin by blocking cell entry. As interesting as these findings may be, they

should not be interpreted to indicate that *Echinacea* species extracts could be an effective replacement for influenza vaccine or oseltamivir to prevent and treat influenza. There are still a number of outstanding issues that need to be addressed regarding the possible therapeutic properties of this health supplement. For example, what is the mode of action of *Echinacea* species extracts? What is the effective oral dose to exert measurable anti-viral activities? How is it metabolized in the body? Would it have to be taken prophylactically to have significant benefit? What are the side effects associated with prolonged intake? Is it also effective against influenza B? Further research is needed to study the anti-influenza effects of *Echinacea* species extracts.

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