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

Purple Paper

2009 H1N1 Influenza Pandemic Debrief Series

Province: Ontario
Public Health Setting: Rural/Urban

What would you do again in a similar public health emergency?

All staff were redeployed to our H1N1 response. Extra staff were hired. Having pre approval for extra expenditures saved time in the actual event. We rented extra space for immunisation clinics We went to all schools to deliver vaccine to children.

What would you NOT do again in a similar public health emergency?

Public Health should not be required to organise alternate treatment centres. We had only our own staff to offer and no funding to do anything until we were into the outbreak. Attempts to engage the local health care sector were only successful when funding was announced.

What was the most difficult situation your organization experienced?

Limited vaccine supply when public demand peaked.

What was the most important lesson learned?

Despite our best efforts we will probably not have enough vaccine in time to alter the course of a novel virus through our community.

What were your most important sources of information?

Ontario MOHLTC. AMOHs from larger Health Units who shared their more in depth analysis with us.

Pandemic pH1N1
Bi-weekly Literature Synthesis
(Weeks of February 7-20, 2010)

Severe Outcomes among pH1N1 Patients

Risk of severe outcomes among patients admitted to hospital with pandemic (H1N1) influenza.
Campbell A et al. *CMAJ. Published online February 16, 2010.*

In this study, researchers from the Public Health Agency of Canada (PHAC) described disease characteristics and risk factors associated with admission to intensive care units (ICU) and death in **Canada** by comparing in-patients who had non-severe pH1N1 disease with those who had severe disease. A severe outcome was defined as admission to ICU or death as a result of pH1N1, while all other hospitalized patients were considered to have a non-severe outcome. Data for all patients admitted to hospital with laboratory-confirmed pH1N1 that were reported to PHAC by the 13 provinces and territories in Canada during the first 5 months of the pandemic (April 26-September 26, 2009) were used for the current analysis.

General epidemiologic features
Of 1,479 pH1N1 patients who were admitted to hospital, 1,171 (79.2%) patients had a non-severe outcome, 236 (16.0%) required intensive care but survived, and the remaining 72 (4.9%) died. The corresponding incidences were 3.47 per 100,000 population, 0.70 per 100,000 population and 0.21 per 100,000 population, respectively.

Age as a risk factor
Overall, patients with a non-severe outcome were younger than those who required intensive care, who in turn were younger than those who died. Whereas the median age was 23 years for all patients, the respective median ages for the three categories of patients were 18 years, 34 years and 51 years. The incidence of hospitalization and ICU admission was the highest among children aged <5 years; however, they had the lowest incidence of death. Conversely, patients aged ≥65 years had the lowest rates of hospitalization and ICU admissions and the highest rate of death.

Aboriginal status as a risk factor
Among 1,088 patients whose Aboriginal status was known, 261 (24%) reported being from the First Nations, Métis or Inuit heritage. In the study population (i.e. hospitalized with confirmed pH1N1), there was no statistically significant difference between the proportion of Aboriginal patients with a non-severe outcome and the proportion of those with a severe outcome. In this population, Aboriginal peoples were not at a greater risk of ICU admission or death than non-Aboriginal patients. However, they experienced a 6.8-fold, 5.8-fold and 4.7-fold higher incidence of non-severe outcomes, severe outcomes and deaths, respectively, than the general population. As the authors note, this paradoxical finding may be due to a higher rate of hospitalization among Aboriginal peoples for milder disease, or to the fact that population-based rates are crude measures that combine both probability of exposure and probability of virulent infection. The authors note that demographic and clinical factors such as younger age distribution and higher prevalence of underlying medical conditions in Aboriginal communities may be at play. Genetic predisposition to more severe outcomes, socio-economic and geographic factors may be additional contributing factors.

Underlying medical conditions as a risk factor
48.2% of all patients reported having at least one underling medical condition – a risk factor shown to be associated with an elevated risk of a severe outcome even after adjustment for age and sex. The risk of a severe outcome was greatest among patients with diabetes mellitus (RR [risk ratio] 2.2, 95% CI [confidence interval] 1.7-2.7) and pre-existing heart disease (RR 2.1, 95% CI 1.6-2.7), followed by those with immunosuppression (RR 1.5, 95% CI 1.1-2.0), renal disease (RR 1.5, 95% CI 1.0-2.1) and lung disease (including asthma) (RR 1.3, 95% CI 1.0-1.6).

Pregnancy as a risk factor
78 (45.9%) of 170 women, who were of child-bearing age (15-44 years), were pregnant during the study period. Pregnant women were not at increased risk of ICU admission or death compared with their non-pregnant counterparts. However, they experienced a higher incidence of hospitalization with a non-severe outcome (12.16 versus 0.94 per 100,000 population), admission to ICU (2.59 versus 0.33 per 100,000 population), and death (0.80 versus 0.05 per 100,000 population), compared with non-pregnant women of child-bearing age.

Time to hospital admission as a risk factor
The median time from symptom onset to hospital admission was 2-3 days. A delay of 1 day in the median time to hospital admission increased the risk of death by 5.5%.

Geography and time as risk factors
The majority of patients reported symptom onset (64.7%) or were admitted to hospital (63.5%) in the month of June 2009. The proportion and median age of patients with a severe outcome did not change significantly throughout the study period. The incidence of non-severe outcomes and ICU admission was highest in Nunavut, the Northwest Territories, Manitoba and Quebec. The incidence of death was highest in Nunavut, Manitoba and Saskatchewan. Caution should be exercised when interpreting the rates for Nunavut and the Northwest Territories because there were only a small number of cases in these jurisdictions.

On the whole, the incidence of hospital admission with laboratory-confirmed pH1N1 was low during the 5 months of the pandemic in Canada. The findings presented in this article are in general agreement with those of the USA, the UK, and Australia.

Pre-Existing Immunity against pH1N1

High frequency of cross-reacting antibodies against 2009 pandemic influenza A(H1N1) virus among the elderly in Finland.
Ikonen N et al. *Euro Surveill. 2010 Feb 4;15(5). pii: 19478.*

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?
Allwinn R et al. *Med Microbiol Immunol. Published online February 17, 2010.*

Two studies were published recently examining the level of pre-existing cross-reactive antibody immunity against pH1N1 in the general population.

In the first study, investigators from **Finland** measured the level of cross-reactive antibodies in 1,031 archived serum samples (collected in 2004 and 2005) from individuals born between 1909 and 2005 using standard laboratory assays. Results showed that the level of cross-reactive antibodies against pH1N1 increased with age, with a considerable proportion of individuals exhibiting a protective level of antibodies (titer ≥ 40) beginning with the birth year 1920. Individuals born between 1909 and 1919 had the highest prevalence of antibodies against pH1N1. Among them, more than 96% had an antibody titer ≥ 10; and more than 55% had a protective antibody titer ≥ 40.

In the second study, researchers from **Germany** tested archived serum samples (collected in 2007 and 2008) from individuals aged 1 year to >60 years. Among 145 serum samples examined, 19 samples demonstrated neutralizing antibody activity against pH1N1, of which 11 belonged to individuals aged >60 years.

All in all, findings of the two current studies are congruent with those from Japan [1], the USA [2] and the UK [3], in that pre-existing immunity against pH1N1 is predominantly observed among individuals aged >60 years.

pH1N1-Associated Mortality in the Elderly

Estimating the impact of the 2009 influenza A(H1N1) pandemic on mortality in the elderly in Navarre, Spain.
Castilla J et al. *Euro Surveill. 2010 Feb 4;15(5). pii: 19481.*

The investigators of this study used surveillance data from primary healthcare, hospitals and laboratories to estimate the number and rate of excess death among the elderly during the circulation of pH1N1 in **Navarre, Spain**. All deaths reported in adults aged ≥65 years in the following 7 periods in 2009 were compared with the average number of deaths (i.e. expected deaths) for the corresponding periods of the 3 preceding years (2006, 2007 and 2008):

1. Weeks 1-8 (2009): Circulation of seasonal influenza viruses that was dominated by the A/(H3N2) strain (94% of all circulating strains)
2. Weeks 9-15 (2009): Sporadic activity of influenza B
3. Weeks 16-23 (2009): No detected influenza activity (inter-seasonal period)
4. Weeks 24-35 (2009): Emergence of pH1N1 (first pandemic wave)
5. Weeks 36-39 (2009): Continued sporadic pH1N1 activity, with low incidence of ILI (pandemic remission period)
6. Weeks 40-49 (2009): Re-emergence of pH1N1 with high incidence of ILI (second pandemic wave)
7. Weeks 50-52 (2009): New remission period with low incidence of ILI and only sporadic detection of pH1N1.

In the period between week 24 and week 52 (2009) when pH1N1 was circulating, there was a statistically significant increase of 4.9% in the number of deaths observed among individuals aged ≥65 years. This was in contrast with the non-pandemic period (weeks 1-23) as no difference was detected between the observed and expected number of deaths. When analyses were performed for the first and second pandemic wave periods, results showed an increase of 9.9% and 5.2% in the number of deaths, respectively. However, only the former reached statistical significance.

NCCID Comments:
This study suggests that excess mortality among older adults may have coincided with periods of pH1N1 circulation in Navarre, Spain. Nevertheless, these findings should be interpreted with caution, since the reported increase in the absolute number of deaths is sensitive to changes in the age demographics of the population. As the authors note, the population aged ≥65 years increased by 3% from the period between 2006 and 2008 to 2009, and the population aged ≥85 years increased by 10%. These changes alone could produce a greater number of deaths, irrespective of other factors. Indeed, when the increase in mortality was reported as the percent change in the rate of mortality, all findings were no longer statistically significant. Furthermore, because comparisons were made between all deaths in 2009 and the expected deaths based on reported numbers in 2006-2008, the actual number of deaths that can be unequivocally attributed to pH1N1 would be difficult to discern.

Simulation Modelling of an Influenza Pandemic

Modelling seasonality and viral mutation to predict the course of an influenza pandemic.
Shi P, Keskinocak P. *Epidemiol Infect. Published online February 17, 2010.*

Being able to forecast the course and severity of an epidemic or pandemic is of utmost importance for guiding public health officials in the rational allocation of resources needed for implementing the appropriate response strategies and surge capacity. In this study, the investigators developed a **simulation model** to examine how seasonal changes in the transmission dynamics (seasonality) and viral mutation may affect the course and magnitude of an influenza pandemic. They described conditions that could lead to 1, 2 and 3 waves in a pandemic situation.

The model was based on the population of the state of Georgia in the USA. Each individual was assigned a set of demographic characteristics according to the 2000 US Census data, and daily movements between households and workplaces or schools according to data from the Georgia Accrediting Commission.

To model seasonality, the two main variables examined were baseline reproductive rate (or basic reproduction number) and the degree of seasonality. In general, more temperate regions tend to have a higher degree of seasonality and a lower basic reproduction number, while more tropical regions tend to have a lower degree of seasonality but a higher basic reproduction number. Combinations of the basic reproduction number (1.5, 1.8 and 2.0) and the degrees of seasonality (0.07, 0.18 and 0.30) were tested to estimate the monthly effective reproduction number over a 12-month period.

To represent viral mutation, a new strain of virus was introduced into the model at various timepoints (30, 60, 93, 120, and 180 days) after the appearance of the first diagnosed case; after which time, a proportion of the resistant population lost their immunity and reverted back to being susceptible (0.5%, 1.5%, 5%, 8%, 10% and 20%).

The impact of the time of introduction of the first identified case on the course of the pandemic was also being modeled. Here, the authors tested scenarios in which the epidemic began in January, February, March, April, May, July or October.

Seasonality scenarios
For different combinations of basic reproduction number and degree of seasonality, a pandemic that began in March and April could result in 2 waves (the first wave in spring and the second in the subsequent autumn/winter), whereas pandemics beginning in January, February, May, July and October had only 1 wave. Overall, the higher the basic reproduction number, the earlier the epidemic peak would occur and the higher the epidemic peak would be. The effect of the degree of seasonality on the magnitude of the pandemic was variable – it had either an enhancing or diminishing effect depending on when the epidemic started.

Viral mutation scenarios
At a minimum, a second wave could only occur if viral mutations arose no earlier than 10 days after the initial epidemic peak, resulting in a daily loss of immunity in >1% of the resistant population. These two conditions were the critical thresholds that determined whether a second wave could result. Overall, after this time threshold, the later the emergence of viral mutations, the later the peak of the second wave would come. Further, the higher the daily loss in the immunity rate, the earlier and the higher the peak of the second wave.

Conditions for three pandemic waves
Using this simulation model, the investigators were able reproduce a three-wave epidemic curve similar to that of the 1918 pandemic. The conditions that led to the three separate waves were:

- Identification of the first case in April
- Basic reproduction number = 1.5
- Degree of seasonality = 0.3
- Emergence of viral mutations 275 days after the initial seed infection
- Daily loss of immunity rate = 1.5%

If you have any comments or questions about the *Purple Paper*, please contact us at nccid@icid.com.

Effectiveness of the Seasonal Influenza Vaccine in the Elderly

Estimating the influenza vaccine effectiveness in elderly on a yearly basis using the Spanish influenza surveillance network – pilot case-control studies using different control groups, 2008-2009 season, Spain.
Savulescu C et al. *Vaccine. Published online February 10, 2010.*

The European Centre for Disease Prevention and Control (ECDC) has recently funded a project to develop an integrative system to monitor seasonal and pandemic influenza vaccine effectiveness in the European Union (EU) and European Economic Area (EEA). This project piloted 5 case-control studies and 2 cohort studies in 6 EU countries during the 2008/09 influenza season. **Spain** participated in this project with a **case-control study** to determine the effectiveness of seasonal influenza vaccines against laboratory-confirmed cases of influenza in the elderly ≥65 years of age. As part of their study, Spanish investigators also estimated the effectiveness of seasonal influenza vaccine using the screening method.

The Spanish Influenza Sentinel Surveillance System (SISSS) consists of over 700 GPs and pediatricians from 16 of 18 regions, covering 2.08% of the entire Spanish population. For the current study, data were collected from 219 sentinel GPs who provided care to 1.74% of the elderly population in 7 participating regions. Respiratory specimens were collected from all patients aged ≥65 years presenting with ILI at sentinel clinics from week 40 (2008) to week 20 (2009) and tested for seasonal influenza by laboratory assays.

For the case-control study, laboratory-confirmed influenza cases were compared with two control groups. The first control group comprised patients with ILI who tested negative for influenza (test-negative controls); the second control group included patients who attended the sentinel clinics and who were devoid of any respiratory symptoms since the beginning of the influenza season (non-ILI controls). GPs used a standardized questionnaire to solicit information from cases and controls regarding:

- Influenza vaccination in the 2008/09 season
- Influenza vaccination in the previous 5 seasons
- Pneumococcal vaccination
- Smoking
- Functional status (whether patients require help for bathing or walking)
- Chronic conditions (diabetes mellitus, cardiovascular diseases, chronic pulmonary disease, congenital or acquired immunodeficiency)
- Hospitalizations for chronic conditions in the past 12 months.

For analyses using the screening method, the proportion of ILI cases who were vaccinated was compared with the vaccination coverage among individuals aged ≥65 years of the participating GPs' catchment population. The latter set of information was obtained from the Ministry of Health after the influenza vaccination campaign.

The influenza activity was moderate in Spain in the 2008/09 season. The epidemic period spanned 9 weeks from week 50 (2008) to week 7 (2009) and peaked in week 1(2009). Among adults aged ≥65 years, the cumulative ILI incidence rate was 603 per 100,000 population, with the maximum incidence rate of 93 per 100,000 population during the peak of the epidemic.

103 ILI patients were recruited for the study, of whom 44 were laboratory-confirmed cases and 59 were test-negative controls. Statistical analysis was performed on a subset of 43 cases and 36 test-negative controls, who were recruited after week 48 (2008) and who had clinical samples collected within 3 days after symptom onset. Results showed that, except for the receipt of the 2008/09 seasonal influenza vaccine (60.5% cases versus 91.7% test-negative controls) and pneumococcal vaccine (58.1% cases versus 85.7% test-negative controls), cases and test-negative controls did not differ significantly in other baseline characteristics. Similarly, cases and non-ILI controls only differed significantly in the 2008/09 seasonal influenza vaccination status (60.5% of 43 cases versus 81.4% of 86 non-ILI controls).

In the analysis using test-negative controls, the crude estimate for the effectiveness of the seasonal influenza vaccine was 86% (95% CI 43%-98%). After adjusting for previous influenza and pneumococcal

vaccination, smoking, functional status, chronic conditions, and previous hospitalizations, the estimate for vaccine effectiveness was 79% (95% CI -26%-96%). In the analysis using non-ILI controls, the crude and adjusted estimates for influenza vaccine effectiveness were 78% (95% CI 33%-93%) and 68% (95% CI -20%-92%), respectively. Lastly, using the screening method, the influenza vaccine effectiveness was estimated to be 18.7% (95% CI -49.8%-55.9%).

NCCID Comments:
This study suggests that the seasonal influenza vaccine is only modestly effective, if at all, in preventing laboratory-confirmed influenza and ILI among individuals aged ≥65 years. After adjusting for confounding, the very wide 95% confidence intervals overlapping the value of 0% are indicative of a high level of uncertainty associated with the point estimate for seasonal influenza vaccine effectiveness, ranging from no effect to near complete protection against seasonal influenza. This may in turn reflect the variability inherent in the data set and the small number of study subjects enrolled. Nevertheless, according to a recently updated Cochrane Intervention Review on the effectiveness of seasonal vaccines in preventing influenza, ILI, hospital admission, complications and mortality in the elderly, uncertainty regarding the efficacy and effectiveness of the seasonal influenza vaccine for people aged ≥65 years remains unresolved [4]. This review highlights the need for more rigorous randomized, placebo-controlled clinical trials. However, given that the seasonal influenza vaccine is globally recommended for the elderly, this study design option for further research may no longer be possible on ethical grounds.

Transmissibility of Oseltamivir-Resistant Seasonal Influenza A Viruses

Household transmissibility and other characteristics of seasonal oseltamivir-resistant influenza A(H1N1) viruses, Germany, 2007-8.
Buchholz U et al. *Euro Surveill. 2010 Feb 11;15(6). pii: 19483.*

It has been shown in animal studies that acquisition and maintenance of oseltamivir resistance by the influenza virus are accommodated by other changes in the virus that may affect its virulence and transmissibility. To delineate the characteristics of oseltamivir-resistant seasonal influenza A viruses in humans, investigators of this **nested case-control study** compared patients with oseltamivir-resistant influenza A/H1N1 virus and those with oseltamivir-sensitive virus from a cohort identified by sentinel physicians in **Germany** during the 2007/08 season.

Of 396 sentinel patients with laboratory-confirmed seasonal influenza infection, 366 (92%) were infected with influenza A/H1N1, none with A/H3N2 and 30 (8%) with influenza B. No influenza B virus isolates were resistant to oseltamivir. Among 366 patients with A/H1N1, 52 (14%) patients were infected with an oseltamivir-resistant A/H1N1 virus, with increasing proportions of patients being identified later in the season, cumulating to 28% in March 2008. There were no statistically significant differences in age, sex and vaccination status between patients with oseltamivir-resistant A/H1N1 viruses and those with oseltamivir-sensitive viruses.

The nested case-control analysis was conducted among 38 and 95 sentinel patients with oseltamivir-resistant (i.e. cases) and -sensitive (i.e. controls) influenza A/H1N1 infections, respectively. These patients were contacted 1-5 months after their original laboratory diagnosis for a telephone interview and were asked to provide information on:

- Pre-existing medical conditions (diabetes, chronic heart disease, chronic lung disease, chronic immunosuppression)
- Travel history
- Oseltamivir treatment or prophylaxis before sample was taken
- Exposure to oseltamivir through household contact
- Complications and outcomes (otitis, pneumonia, hospitalization, death, duration of sick leave in days, number of days confined to bed).

Results showed that there were no statistically significant differences in any of the above between the two groups.

Additionally, information on household size and the occurrence of ILI in the household on the same day or 5 days before or after onset of illness in the sentinel patient was also elicited. The median number of persons in the study households was 4; there was no statistically significant difference in this

respect between the two groups. It was estimated that the overall secondary attack rate in households was 25.4%. The secondary attack rate in households whose patients had oseltamivir-sensitive influenza A/H1N1 infection was 26.2%, whereas the secondary rate for households with oseltamivir-resistant patients was 22.8%. This difference between the two groups also did not reach statistical significance. Finally, comparison between the oseltamivir-resistant and -sensitive groups showed that none of the following variables appeared to be associated with secondary household influenza transmission:

- Oseltamivir resistance of the sentinel patient
- Treatment of the sentinel patient with oseltamivir
- Male sex of the sentinel patient
- Date of symptom onset of the sentinel patient
- Household of two persons.

NCCID Comments:

This study suggests that both oseltamivir-resistant and -sensitive influenza A/H1N1 virus strains isolated in Germany during the 2007/08 season were pathogenic and could be transmitted to a similar degree. Nevertheless, the validity of this conclusion should be considered alongside the limitations of this study. One of the major limitations of this study was its small sample size. Consequently, this study may not have the adequate statistical power to detect subtle differences (if they exist) between the two study groups. Recall bias may be introduced into the data set due to the long delay between diagnoses of the primary patients and the telephone interview. Household cases were not laboratory-confirmed but identified based on self-reported symptoms. Furthermore, no information was available regarding the possible differential immunity against the seasonal A/H1N1 influenza virus between household contacts of the oseltamivir-resistant and -sensitive groups. This variable has important implications on the outcomes being measured, and ultimately the conclusion being made by the investigators, and should have been addressed accordingly. Further research on how acquisition of oseltamivir resistance affects other characteristics of the influenza virus is needed.

Notable Publications

Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection.
To KK et al. *Clin Infect Dis. Published online February 5, 2010.*

Seasonal and pandemic human influenza viruses attach better to human upper respiratory tract epithelium than avian influenza viruses.
van Riel D et al. *Am J Pathol. Published online February 18, 2010*.

The Spanish influenza pandemic in occidental Europe (1918-1920) and victim age.
Erkoreka A. *Influenza Other Respi Viruses. 2010; 4(2):81-89.*

Evaluation of Southern Hemisphere influenza vaccine recommendations.
Richard SA et al. *Vaccine. Published online February 10, 2010.*

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[1] Itoh Y et al. In vitro and in vivo characterisation of new swine-origin H1N1 influenza viruses. *Nature. 2009; 460(7258):1021-1025.*

[2] Hancock K et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med. 2009; 361:1945-1952.*

[3] Miller E et al. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet. Published online January 21, 2010.*

[4] Jefferson T et al. Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews* 2010, Issue 2. Art. No.: CD004876. DOI: 10.1002/14651858.CD004876.pub3.

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