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

Purple Paper

2009 H1N1 Influenza Pandemic Debrief Series

Organization: First Nations and Inuit Health
City, Province: Edmonton, Alberta
Setting: Rural/ Northern/ Isolated

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

A) Prompt communication with population;
B) Seamless coordination between our federal regional FNIH team, the community staff and the provincial public health authorities, including
   1. the prepositioning of antiviral and other supplies in remote and isolated communities;
   2. clear agreements on roles and responsibilities with regard to vaccine acquisition and distribution to communities, and,
   3. FNIH's participation on provincial EOCs [*NCCID note: Emergency Operations Centres*];
C) Keeping population posted via information bulletin and videoconferencing as needed;
D) Dedicated and organized travel nursing team for surge capacity at communities of needs;
E) ILI assessment services in communities with competent on call staff to guide community staff;
F) Training sessions with staff on use of algorithms for antivirals;
G) Strong support by the organization administration and by FN leadership.

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

Respond to so many requests for information by other agencies through myriads of emails

What was the most difficult situation your organization experienced?

The multiple attempts and requests for information from several sources distracting from the response effort

What was the most important lesson learned?

Timely and appropriate communication with FN population living on reserve

What were your most important sources of information?

Provincial health department and National PHAC

Pandemic pH1N1 Weekly Literature Synthesis (Week of January 31 – February 6, 2010)

Seasonal Influenza Vaccine in Infants

Safety and immunogenicity of trivalent inactivated influenza vaccine in infants: a randomized double-blind placebo-controlled study.
Englund JA et al. *Pediatr Infect Dis J. 2010; 29(2):105-10.*

Children aged <6 months are highly susceptible to illness and complications associated with influenza, yet no vaccine is licensed for this population. To explore the possibility of extending the use of existing trivalent inactivated influenza vaccines (TIV) to infants, the authors of this study examined the safety and immunogenicity of seasonal TIV in children 6-12 weeks of age in a **prospective, multicentre, double-blind, randomized, placebo-controlled clinical trial** in the **USA**.

Only healthy children of 6-12 weeks of age at the time of enrolment (September-December 2005) were eligible for inclusion. They received 2 doses of TIV (Fluzone®, sanofi pasteur) or placebo (sterile saline solution) 1 month apart. The TIV used in this study was licensed for the 2005/06 influenza season in North America. Each 0.25mL dose contained 7.5 micrograms of hemagglutinin of the seasonal influenzas A/H1N1, A/H3N2 and B; and is preservative-free. Routine childhood vaccines were administered concomitantly with TIV at the first visit and without TIV at 4 and 6 months of age. These concomitant childhood vaccines included diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine (DTaP), *Haemophilus influenzae* type B conjugate vaccine (HiB), pneumococcal conjugate vaccine (PNC), inactivated polio vaccine (IPV), and hepatitis B vaccine (HepB).

Vaccine safety assessment was based on adverse events reported by parents. Safety outcomes included immediate reactions at the time of

vaccination, solicited local and systemic reactions for 7 days, unsolicited adverse events for 28 days and serious adverse events.

The induced antibody titer against each of the seasonal influenza vaccine strains in vaccinees was determined by laboratory assays. Vaccine immunogenicity was in turn inferred by 2 standard antibody measures: geometric mean titer (GMT) and seroprotection rate (proportion of vaccinees with titers ≥ 1:40 post-immunization). Antibody responses to childhood vaccines were also determined using the same antibody measures, but each childhood vaccine had its own predefined seroprotective criteria.

A total of 1375 infants receiving at least 1 injection of TIV or placebo were included for safety analysis. There was no difference in the demographics (age, sex, race, ethnicity, and history of maternal influenza vaccine) between the TIV and placebo groups. Similar proportions of both study groups received the three doses of DTaP, HiB, IPV and PNC vaccines. Use of antibiotics and anti-pyretics was also similar in both groups. In terms of the safety profile of TIV, no significant differences were seen between TIV and placebo recipients in the frequencies of reported adverse effects. Local injection site reactions were the most common among subjects of both groups, but these tended to be mild in intensity and resolved within 2 days. Fever ≥38°C within 3 days of vaccination was observed in 11.2% and 11.7% of TIV and placebo groups, respectively. The incidence of local injection site reactions and fever was significantly reduced following the second dose of TIV or placebo. Unsolicited adverse events occurring within 28 days and serious adverse events were also comparably reported in the two groups, and their incidence was not significantly different. Two subjects in the TIV group experienced unsolicited adverse events within 20 minutes of vaccination: one with non-severe allergic reaction (also the only TIV-related serious adverse event) and the other with colic.

A total of 1096 infants (717 in TIV group, 349 in placebo group), who received at least 1 dose of TIV or placebo and had a valid serology result at 4 or 7 months of age, were included for immunogenicity analysis. As above, the baseline characteristics of the TIV and placebo groups were not significantly different. Compared to placebo recipients, antibodies against all three influenza vaccine strains significantly increased in subjects of the TIV group, although better responses to influenza A strains were observed. The reciprocal GMT to A/H1N1, A/H3N2 and B were 33, 95, and 11 in TIV recipients; and 7, 9, and 5 in placebo recipients. Following 2 doses of TIV, 90.2% of TIV recipients had a seroprotective antibody titer of ≥1:40 to at least 1 vaccine strain and 49.6% to 2 vaccine strains, compared to 16.4% and 0.9% in the placebo group. Lastly, antibody responses to all childhood vaccines were comparable in both TIV and placebo groups, indicating that concomitant immunization against childhood diseases did not interfere with the development of anti-influenza antibody response, and vice versa.

All in all, this study demonstrates that TIV is safe and immunogenic in infants. Administration of TIV to infants at as early as 2 months of age could enhance protection from influenza in this vulnerable population. Concomitant administration of childhood vaccines with TIV does not appear to interfere with the development of anti-influenza immunity, and vice versa, but may increase vaccine uptake.

Household Responses to School Closures

Household responses to pandemic (H1N1) 2009-related school closures, Perth, Western Australia. Effler PV et al. *Emerg Infect Dis. 2010; 16(2):205-11.*

On June 7, 2009, upon laboratory confirmation of pH1N1 in a number of school children from Perth, Australia, the Department of Health advised 3 schools to cancel classes for the following week (June 8-14, 2009). Among these schools, 1 public school closed entirely. The 2 remaining private schools cancelled classes for grade 5 and grades 5-7, in which at least 1 student was a confirmed pH1N1 case. The authors of this study examined the effect of school closure on families – parental opinion regarding school closures, childcare arrangement and activities of students during school closure – by surveying parents of all students excluded from attendance.

In this study, a case-patient was defined as a student with a laboratory diagnosis of pH1N1. A contact was

defined as a student who had been in a classroom with a case-patient for ≥4 hours or who had had another period of close physical proximity (e.g. sitting within 1 m of the case-patient for at least 15 minutes) during the case-patient's infectious period (1 day before the onset of symptoms and 7 days after). All other students, who were affected by the school closure but did not meet the criteria for either a case-patient or contact, were defined as school peers.

Of 402 surveys sent to households affected by the school closure, 233 (58%) were returned. Among these, 12 (5%) were from households of case-patients who instigated the recommendation for school closure, 143 (61%) were from households of contacts, and the remaining 78 (34%) were from household of peers.

172 (74% of 233) students reported spending time outside the home in a total of 860 out-of-home activities during the school closure, with an overall mean of 3.7 activities/student/week. The number of out-of-home activities reported by individual students ranged from 0 to 24 (median 3 activities). Activities engaged by students included sporting events, outdoor recreation, shopping, and parties.

There was statistically significant difference in the proportion of case-patients (42%), contacts (66%), and peers (92%) who reported going out of the home ≥1 time during school closure. There was also statistically significant difference in the mean number of out-of-home activities among students of these three groups. Case-patients, contacts and peers reported an average of 0.8, 2.9 and 5.6 out-of-home activities/student/week, respectively.

Of 202 contacts and peers who did not develop ILI or upper respiratory infection over the closure period (asymptomatic students), 91 (45%) parents reported taking ≥1 day off work to care for their child (median 3 days; range 1-5 days). In addition, 71 (35%) parents of asymptomatic students reported having to make alternate childcare arrangements for a median of 2 days (range 1-5 days). 20 (10%) students cared for themselves at home for at least a portion of the closure period. Of 202 asymptomatic and 31 ill students, 38 (19%) and 2 (6%), respectively, were cared for in a setting with children other than their siblings.

In terms of parental opinion about school closures, of 233 parents who responded, 110 (47%) parents thought the school closure was appropriate, 76 (33%) thought it was inappropriate, and the remaining 47 (20%) were unsure. The proportion of parents who thought that the school closure was appropriate was highest among parents of case-patients (92%), followed by parents of contacts (48%), and peers (39%). Parental opinion about the appropriateness of the school closure was also significantly associated with the frequency of the students' out-of-home activities. Students of parents who thought the school closure was appropriate had a mean of 2.8 out-of-home activities; those of parents who thought the school closure was inappropriate had a mean of 4.7 out-of-home activities; finally, students of parents who were unsure had a mean of 4.3 outings.

NCCID Comments:

School closures, as a social distancing measure to mitigate the spread of pH1N1, has been a contentious issue in public health. This is largely due to the fact that the effectiveness and the unintended ripple effects of school closures on society at large are difficult to measure. In order for school closures to be effective, one would expect stringent compliance on the part of students to remain home during the closure period. However, as this study indicates, such an assumption is not realistic. In fact, this study shows that, among 233 students from 3 schools which had imposed various extent of attendance suspension, each student had spent time outside of the home on an average of nearly 4 occasions during the 7-day closure period. Some students even reported a maximum of 24 outings. Furthermore, parents indicated that some students were cared for in a setting with other children from the community. Because no information was available regarding the baseline level of out-of-home activities among students who were not subject to the school closure, it is uncertain whether the reported level of out-of-home activities involving "float" students actually represented a reduction from "normal" levels. In spite of this, it is clear that some of these out-of-home activities and the settings in which they were held were potentially conducive to the transmission of influenza. Further research is warranted, as the effectiveness of school closures in reducing transmission of influenza

continues to be elusive at this juncture. Moreover, many often-neglected social and ethical issues associated with school closures should also be addressed.

Environmental Cleaning

Effectiveness of common household cleaning agents in reducing the viability of human influenza A/H1N1.
Greatorex JS et al. *PLoS One. 2010; 5(2):e8987.*

During influenza epidemics and pandemics, the majority of people who become ill will likely be nursed at home. Therefore, simple methods for limiting the spread of influenza within the home that are at the disposal of the general public are important. The investigators of this study examined the effectiveness of a range of commercially-available household cleaners and wipes in killing and reducing the viability of a human seasonal influenza A/H1N1 virus.

A range of household cleaners were tested at different concentrations:

- Bleach: 1%
- Malt vinegar: 1%, 10%, 50%
- Dishwashing detergent: 0.01%, 0.1%, 1%

Various wipes and tissues were also tested by extracting their cleaning agents in cold sterile water rinses. These included:

- Branded antibacterial wipes
- Multi-surface furniture wipes
- Toddler wipes
- Anti-viral tissues.

In all experiments, a fixed volume of diluted household cleaners and wipe/tissue solutions were combined with a diluted influenza sample, and then examined by laboratory assays immediately (as a measure of rapid inactivation) or after 60 minutes of incubation (to simulate prolonged contact). Hot water (55°C) alone was used as the negative control.

Results showed that rapid treatment of the virus with hot water had little effect, but prolonged incubation at 55°C abolished any detectable infectivity. Except for 1% vinegar, all household cleaners at the above-indicated concentrations were effective rapid disinfectants. 1% vinegar could only reduce viable virus to levels below detection after prolonged exposure. Results for wipes/tissues were mixed. While toddler wipes were not virucidal in either rapid or prolonged treatment scenarios, antibacterial wipes and anti-viral tissues showed an instantaneous effect in inactivating the virus. Multi-surface furniture wipes only showed a complete virucidal effect after prolonged incubation.

The experimental methods used here did not necessarily replicate real-life domestic cleaning conditions. For example, routine surface cleaning rarely permits thorough mixing and exposure between cleaning agents and contaminating influenza viruses on fomites. Nevertheless, this study demonstrates that several common household cleaners can effectively inactivate influenza viruses when industrial virucidal products are not available.

Effects of Oseltamivir on Seasonal Influenza

Effects of oseltamivir treatment on duration of clinical illness and viral shedding and household transmission of influenza virus.
Ng S et al. *Clin Infect Dis. Published online January 13, 2010.*

This article reports the effect of oseltamivir treatment on symptom duration, viral shedding, and secondary household transmission of seasonal influenza. It presents findings of a **secondary analysis of data from a community-based randomized controlled trial** of the use of face masks and enhanced hand hygiene to minimize household transmission of influenza virus. The secondary analysis was possible due to an unexpectedly high-level of anti-viral use among study participants. The current study focused on the clinical effects of oseltamivir only.

Study participants were recruited from February to September 2007 and from January to September 2008 from 45 public and private outpatient clinics in **Hong Kong**. Subjects were enrolled if they tested positive for influenza A or B using a rapid test; were index patients in a household, who reported at least 2 symptoms of acute respiratory illness (ARI) with symptom onset within 48 hours; and lived with at least 2 other individuals, none of whom had reported ARI symptoms during the past 14 days. Decision on oseltamivir treatment was **not randomized** and was left to the discretion of the

treating physician. All medication prescribed to the index patients, including oseltamivir and any other drugs for symptomatic relief, were recorded at recruitment sites and confirmed during subsequent home visits. Home visits were made within 48 hours of recruitment, and an additional 2 or 3 visits were scheduled during the subsequent 7 days in 2007 and 10 days in 2008. All index patients and their household contacts were asked to record their body temperature and any systemic and respiratory signs and symptoms once daily until the final home visit. During each visit, nasal and throat swabs were also collected from all household participants for laboratory testing.

Of the 384 index patients who were laboratory-confirmed cases of seasonal influenza and had complied with the requirements of the clinical trial, 90 (23%) were treated with oseltamivir. Overall, the baseline characteristics were comparable between patients who received oseltamivir treatment and those who did not – with the exception that there were more febrile patients and fewer patients prescribed anti-pyretics or anti-histamines in the oseltamivir-treated group. This difference, however, was only marginally significant.

Duration of influenza symptoms

The median duration of illness was 9 days for the oseltamivir-treated group and 11 days for the "no treatment" group. Compared to index patients who were not treated, patients who received oseltamivir within 24 hours of symptom onset experienced a statistically significant reduction in time to alleviation of all influenza symptoms, fever, and respiratory symptoms by 44% (95% confidence interval [CI] 24%-58%), 47% (95% CI 35%-56%) and 44% (95% CI 23%-58%), respectively. When oseltamivir was administered at 1-2 days or >2 days after onset of symptoms, time to alleviation of all symptoms or respiratory symptoms was similarly reduced compared to no treatment; however, the observed reduction was no longer statistically significant. Oseltamivir did not appear to have any beneficial effect in shortening the duration of fever when given >1 day after symptom onset.

Duration of viral shedding

The median duration of viral shedding among study subjects was 6 days. Although viral shedding appeared to resolve sooner among patients who received oseltamivir treatment within 24-48 hours of symptom onset, the significance of this finding was not statistically significant.

Secondary household transmission

Among 331 households with a single index patient, 80 of 989 household contacts had laboratory-confirmed seasonal influenza infection. This was equivalent to an overall secondary attack rate of 8.1% (95%CI 6.5%-10.0%). Compared to the "no treatment" group whose secondary attack rate was 8.7% (95% CI 6.8%-11.0%), the secondary attack rate in household contacts of index patients who were administered oseltamivir within 24 hours, 24-48 hours, and >48 hours after symptom onset was 4.7% (95%CI 1.0%-13.0%), 6.0% (95%CI 2.5%-12.0%), and 8.1% (95%CI 1.5%-19.0%), respectively. This trend of increasing secondary attack rate with increasing delay to oseltamivir treatment after symptom onset was statistically significant. Increasing delay to oseltamivir treatment was also loosely associated with an increased risk in household contacts of developing laboratory-confirmed influenza or clinical influenza. This finding suggests that treating index patients early with oseltamivir may confer some degree of protection to their household contacts; however, neither the individual point estimates nor overall trend reached statistical significance.

NCCID Comments:

As demonstrated in this study, the effect of oseltamivir in reducing the duration of influenza symptoms, duration of viral shedding and secondary household transmission was the greatest when the anti-viral was administered within 24 hours of symptom onset – a time frame that is considerably shorter than the recommended 48 hour window. This observation was likely due to the fact that nearly 90% (345 of 384 subjects) and 84% (324 of 384 subjects) of all index patients were prescribed anti-pyretics and anti-histamines for symptom relief. Although only a small proportion of index patients receiving oseltamivir were also prescribed anti-pyretics and anti-histamine, the effect of oseltamivir in shortening duration of influenza symptoms would likely be masked when comparisons were made between treatment and control groups. This may also explain why oseltamivir did not show any beneficial effect in shortening the duration of fever when given >24 hours after the onset of symptoms.

In addition, the effectiveness of oseltamivir may be further underestimated due to possible resistance among circulating seasonal influenza viruses; even though the author did note that the level of resistance was rare during the 2007 study period and low during the 2008 study period (12.5% of 2007/008 seasonal influenza A/H1N1 isolates were resistant to oseltamivir). Despite these limitations, this study suggests that oseltamivir has modest effectiveness of in treating influenza at best and is in close agreement with the conclusion of a recently updated Cochrane systematic review [1]. The effectiveness of oseltamivir treatment against symptomatic influenza continues to be a subject of much debate.

Epidemiology of pH1N1

Rhinoviruses delayed the circulation of pandemic influenza A(H1N1) 2009 virus in France.
Casalegno JS et al. *Clin Microbiol Infect. Published online January 28, 2010.*

It was predicted that pH1N1 would reach epidemic levels in Europe by week 36 (first week of September) 2009. However, in France, the spread of pH1N1 was unexpectedly slow. From week 36-43, only sporadic pH1N1 activity was reported; and widespread pH1N1 activity indicative of an epidemic did not occur until week 44 (mid-late October). It was speculated that heightened circulation of human rhinovirus (HRV) beginning in early September might have been responsible for delaying the surge of pH1N1. To test the hypothesis, the authors of this study reviewed laboratory results for respiratory specimens obtained from children presenting with ILI in the emergency department of a pediatric hospital in **France** from week 36-48. **Retrospective statistical analyses** were performed to determine the association between HRV and pH1N1.

The mean age of the patient population was 3.8 years (standard deviation [SD] 4.4 years). Among the patients, 55.3% were boys. 73.2% and 4.6% of the patients were admitted to the emergency unit and intensive care unit, respectively. Of 2121 samples tested for pH1N1, 1456 (68.6%) samples were also tested for HRV. At least one virus was detected in 925 (43.6% of 2121) specimens; of which, co-infection was observed in 15 (0.7% 2121) samples.

The HRV epidemic began in week 37 (relative frequency 20.6%), peaked in week 40 (relative frequency 36.8%) and gradually waned by week 45 (relative frequency 4.6%). By contrast, the pH1N1 epidemic began in week 43 (relative frequency 18.8%), peaked in week 47 and remained active in week 48, by which time the HRV epidemic had largely subsided. Thus, HRV and pH1N1 co-circulated during the overlapping period between week 43 and week 47, with respective relative frequencies of 17.7% and 42.9%.

Statistical analysis showed an inverse relationship between the detection of HRV and pH1N1 in the pediatric clinical samples. The odds ratio for the likelihood of detection of pH1N1 in HRV-positive samples was 0.15 (95% CI 0.09-0.24) for the entire study period (weeks 36-48). During co-circulation of HRV and pH1N1 (weeks 43-47), the odds ratio for the likelihood of detection of pH1N1 in HRV-positive samples was 0.17 (95% CI 0.10-0.30). The observed inverse relationship between HRV and pH1N1 was statistically significant irrespective of the time period and age group analyzed. Therefore, the results of this study suggest that the presence of HRV might have reduced the risk of pH1N1 infection in early autumn in France and indirectly interfered with the spread of the impending epidemic.

As the authors note, the main limitation of this study was that the analyzed samples were primarily derived from a pediatric cohort. It would be of interest to determine if the findings are applicable to the general population.

pH1N1 Outbreak on a Farm

An investigation into human pandemic influenza virus (H1N1) 2009 on an Alberta swine farm.
Howden KJ et al. *Can Vet J. 2009; 50(11):1153-1161.*

This article was originally published in November 2009 and documents the investigation of a pH1N1 outbreak on a swine farm in Alberta during the first pandemic wave. The investigation was undertaken by the Canadian Food Inspection Agency (CFIA) and Alberta Agriculture and Rural Development (ARD).

On April 28, 2009, the owner of a swine operation in Alberta informed his herd veterinarian of an acute onset cough in his animals. Upon reporting to the

CFIA and ARD, the farm was put under quarantine under the *Health of Animals Act* and a full epidemiological investigation was conducted. Unequivocal diagnosis of pH1N1 was confirmed by laboratory tests on May 2, 2009 and the findings were immediately conveyed to the World Organization for Animal Health (OIE). Based on initial sampling in affected areas of the swine farm, the prevalence of pH1N1 was estimated to be 87.5% (95% CI 69.0%-95.7%). By this time, however, pH1N1 had already spread throughout the farm as ILI was apparent in animals in all areas of the facility. ILI resolved within 4-5 weeks from its initial onset on April 28, 2009. Despite an uneventful clinical recovery of the animals, no purchasers would accept animals from this farm after the quarantine was lifted – the primary reasons being unfounded concerns about food safety and marketability. Due to looming overcrowding issues and economic distress, the owner of the farm made the decision to depopulate the entire herd. The culling of the herd was not ordered by either the CFIA or ARD on the grounds of animal or human disease concerns. As a result, none of the animals from this farm entered the human food or animal feed chain.

The source of the pH1N1 virus in this outbreak was determined to be a contractor who was hired to work on the ventilation system in areas of the facility where first signs of ILI among the animals were recognized. This individual had recently travelled to Mexico and exhibited ILI while working in the barn on April 14, 2009. Based on the evidence from serological tests, this individual was confirmed to be a case of pH1N1. Although this individual appeared to be the most likely source for the pH1N1 outbreak, the possibility of alternate or additional sources of the virus could not be ruled out. This was because a number of community members, who had direct or indirect contact with the swine herd, also had a recent travel history to Mexico and ILI prior to the first observed clinical signs in the swine herd. Furthermore, zoonotic transmission to 2 outbreak investigators and to other community members with an epidemiological link to the farm was suspected, as these individuals became ill after the start of the outbreak in swine.

Notable Publications

Is oseltamivir (Tamiflu®) safe? Re-examining the Tamiflu 'ado' from Japan.
Okamoto E. *Expert Rev Pharmacoecon Outcomes Res. 2010 Feb; 10(1):17-24.*

Cost-effectiveness of Pharmaceutical-based Pandemic Influenza Mitigation Strategies.
Newall AT et al. *Emerg Infect Dis. 2010 Feb; 16(2):224-30.*

Logistical feasibility and potential benefits of a population-wide passive-immunotherapy program during an influenza pandemic.
Wu JT et al. Proc *Natl Acad Sci U S A. Published online February 1, 2010.*

References

[1] Jefferson T *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ 2009; 339:b5106.*

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