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

Purple Paper

Pandemic H1N1 Weekly Literature Synthesis
(Week of November 8-14, 2009)

Welcome to the first issue of *Purple Paper* – NCCID's Pandemic H1N1 Weekly Literature Synthesis! This newsletter will summarize weekly peer-reviewed H1N1 literature pertinent to public health, and contextualize research findings to shed light on the Canadian situation. We hope this newsletter will fulfil some of the information needs of public health practitioners and will be of interest to our audiences.

Personal Protective Equipment

Surgical Mask vs N95 Respirator for Preventing Influenza Among Health Care Workers: A Randomized Trial
Loeb M *et al*. *JAMA. 2009; 302:1865-1871.*

The effectiveness of surgical masks in preventing the spread of influenza has always been a contentious issue. In this **Canadian** study, the investigators attempted to answer this question by using a **randomized-controlled trial** study design to directly compare the effectiveness of surgical masks to N95 respirators. Nurses who worked in emergency departments, medical units, and pediatric units in 8 Ontario tertiary care hospitals were randomly assigned to either surgical mask or N95 study group. They were asked to use the surgical mask or N95 respirator when caring for patients with febrile respiratory illness during the study period. The primary outcome was laboratory-confirmed influenza cases. Secondary outcome was laboratory-confirmed cases of other respiratory infections (i.e. adenovirus, respiratory syncytial virus, metapneumovirus, parainfluenza virus, rhinovirus-enterovirus and coronavirus). Both investigators and laboratory personnel had no knowledge of the identity of nurses allocated to either study groups. To assess compliance of participants, inconspicuous auditors were sent to a number of participants' hospital units to directly observe and record the type of protective equipment worn by the participants.

Of the 446 eligible nurses enrolled between September 23 and December 8, 2008, 225 were assigned to the surgical mask group and 221 to the N95 respirator group. The demographics of participants in both groups were similar. Follow-up and compliance of assigned protective equipment usage was also very high. There was no statistically significant difference in the incidence of laboratory-confirmed influenza and other respiratory viruses between the surgical mask and N95 respirator users. Based on preset statistical criteria, the surgical mask was not inferior to the N95 respirator in preventing transmission of influenza and other respiratory infections examined in this study.

Findings from this **well-designed and well-executed** study suggest that protection with surgical masks against influenza and other respiratory viral infections appears to be similar to N95 respirators. During periods when N95 respirators are in short supply or unavailable in some countries, making surgical masks available to health care workers could protect them from contracting influenza from symptomatic patients. However, the authors of this study cautioned against the overly-generalized usage of surgical masks. In settings where there is a high risk of aerosolization, use of N95 respirators would be prudent.

Mitigation Strategy Simulation Modelling

Modelling mitigation strategies for pandemic (H1N1) 2009
Gojovic MZ *et al. CMAJ. 2009; 181:673-680.*

To assess the effectiveness of vaccination, closure of schools and daycares, and anti-viral drug treatment strategies on mitigating the spread of H1N1 in a community, a group of **Canadian** scientists developed a **simulation model** of an H1N1 outbreak in a structured population based on demographic data from London, Ontario and current H1N1 pandemic influenza epidemiologic data. Various scenarios of each mitigation strategy were considered and analyzed in 630 possible combinations.

In general, this simulation model demonstrated that closure of schools and daycares alone was effective in reducing the attack rate of influenza in a community, especially if applied early in the outbreak, and regardless of the use of vaccination. The converse was also true – vaccination alone was effective in reducing influenza attack rates with or without closure of schools and daycare. However, the effectiveness of vaccination was compromised when there was a delay in vaccination. For instance, in the setting of school and daycare closure, vaccinating 60 days after the outbreak began was as ineffective as no vaccination at all. On the other hand, if vaccination of 60% of the population could be achieved before the outbreak, closure of schools and daycares would become unnecessary in reducing influenza attack rates.

NCCID Comments:

Although the simulation model suggests that there may be some benefits to be had from proactive closure of schools and daycares to slow the spread of infection, it did not fully address the consequences and social costs of such measures. For example, as the authors note, it did not account for other ways that “float” students would congregate in different venues that could also promote spread of H1N1 infection if schools are closed. Moreover, societal disruptions caused by school and daycare closures need to be balanced against potential benefits.

Another limitation of this simulation model was the assumption of general vaccination, which did not reflect targeted vaccination of priority groups implemented across Canada.

Nonetheless, although simulation models are often simplistic, they do provide insights at times of uncertainty.

Epidemiology of the H1N1

Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA
White LF *et al. Influenza and Other Respiratory Virus 2009; 3:267-276.*

The two epidemiological parameters that are crucial for understanding the dynamics of any infectious disease are reproduction (or reproductive) number and serial interval. Reproduction number, R_o, measures how broadly a pathogen spreads. In more practical terms, R_o represents the average number of secondary cases generated by a typical case in a susceptible population. If $R_o < 1$, transmission of infection cannot be sustained. If $R_o > 1$, an epidemic may occur. As such, the higher the R_o, the more difficult it is to control the epidemic. On the other hand, serial interval measures how fast a pathogen spreads. It represents the time between consecutive infections – in other words, time between onset of symptoms in an index case and a secondary case. Together, reproduction number and serial interval characterize the growth rate of an epidemic.

In this study, the authors used data from the Centers for Disease Control and Prevention (CDC) on reported H1N1 cases during the first pandemic wave in the **USA** to estimate the reproduction number and serial interval of H1N1. Using the raw CDC data, the authors estimated the reproduction number to be 2.2-2.3 and the mean serial interval to be 2.5-2.6 days. Furthermore, after statistically compensating for varying levels of certainty associated with the data sets of the reported cases in the early vs. late phase of the first wave, the authors reported an adjusted estimate of 1.7-1.8 for reproduction number and 2.2-2.3 days for the mean serial interval.

Compared to seasonal influenza, whose reproduction number had been estimated to be 1.3 (with year-to-year variability of 0.9-2.1) [1] and mean serial interval to be 3.6 days [2], this study suggests that although a person with H1N1 can infect a similar number of people when s/he is communicable, H1N1 is spread much faster because the time between successive generations of infection is much shorter. Therefore, H1N1 can infect an overall larger number of people than seasonal influenza within a given time period. It is expected that these estimates are, to a great extent, applicable to the Canadian setting. However, it should be emphasized that the reproduction number and serial interval of an infectious disease are not static. These measures change as the pathogen continues to evolve in response to its changing environment, for example, behaviour and susceptibility/immunity of the host population, public health control strategies, seasonal change and change in the physical environment. Continued monitoring of the growth of the current pandemic in different settings is necessary to determine the range of reproduction numbers and serial intervals of the influenza A/H1N1 in the second wave.

Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009
Jain S *et al. N Engl J Med 2009; 361:1935-1944.*
Critically Ill Patients With 2009 Influenza A (H1N1) Infection in Canada
Kumar A *et al. JAMA 2009; 302: 1872-1879.*
Critically Ill Patients With 2009 Influenza A (H1N1) Infection in Mexico
Domínguez-Cherit G *et al. JAMA 2009; 302: 1880-1887.*
Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A (H1N1) Infection in California
Louie JK *et al. JAMA 2009; 302:1896-1902.*
Pandemic (H1N1) 2009: A clinical spectrum in the general paediatric population
Larcombe PJ *et al. Arch Dis Child. Published online November 10, 2009*

Five **case series** were published last week reporting the characteristics of patients infected with H1N1 who were hospitalized or had succumbed to their illness in the first pandemic wave in **Canada, the USA, Mexico and Australia**. Although the setting of each study was unique, generally consistent findings were observed.

In the four studies which examined hospitalized H1N1 patients from the general population in Canada, the USA and Mexico, the majority of patients consisted of young adults – the range of median age of these four studies was between 21 and 44 years. With the exception of the Mexican study, which had very few pediatric patients, approximately 33% of all hospitalized patients were under the age of 18.

The symptoms of hospitalized H1N1 patients were generally similar to those reported during peak periods of seasonal influenza. In all five studies, including the Australian study which primarily focused on pediatric H1N1 patients, most patients presented with fever and cough. Whereas diarrhea and vomiting have only occasionally been reported in patients ill with seasonal influenza, these symptoms were much more prominent in patients with H1N1.

The majority of patients (42-98%) had at least one underlying medical condition. Asthma (except in the Mexican patient group), followed by obesity, were the two most common underlying medical conditions across all studies. Since most obese patients also had other underlying medical conditions, further analysis is needed to delineate the link between obesity and an increased risk of influenza-related complications. As with seasonal influenza, the proportion of pregnant women was over-represented in the H1N1 patient cohort as compared to the general population.

Pre-Existing Immunity to H1N1

Cross-Reactive Antibody Responses to the 2009 Pandemic H1N1 Influenza Virus
Hancock *K et al. N Engl J Med 2009; 361:1945-1952.*

To assess the level of pre-existing immunity to 2009 H1N1 in the **US population**, investigators in this study measured the level of cross-reactive antibodies in frozen serum samples collected after previous influenza infection or vaccination from people of different age groups. Collected serum samples were from:

1. Children aged 6 months to 9 years before and after seasonal influenza vaccination
2. Adults aged 18 to 64 years before and after seasonal influenza vaccination
3. Older adults aged 60 years and over before and after seasonal influenza vaccination
4. Anonymous donors born between 1880 to 2004, including a subset of subjects who had received the 1976 influenza A/H1N1 vaccine.

Cross-reactive antibody response in the different groups was examined by determining if serums could inhibit 2009 H1N1 infection of susceptible cells in laboratory experiments.

Results showed that most children and young adults born after 1980 had little or no cross-reactive antibody response against 2009 H1N1. Vaccination with recent seasonal influenza vaccines did not induce cross-reactive antibody responses to H1N1 in any age groups.

This is in contrast to the observations in older adults. Approximately one-third of older adults who were born before 1950 had some degree of cross-reactive antibody response against 2009 H1N1. Among subjects in a subset of this group who were at least 25 years of age at the time when the sample was collected and had prior natural infection, subsequent vaccination against the 1976 influenza A/H1N1 probably led to the generation or boosting of cross-reactive antibody responses to 2009 H1N1. However, seasonal influenza vaccination appeared to have only a limited boosting effect.

The findings of this study are consistent with the observation that the majority of 2009 H1N1 cases occur in children and young adults, as the lack of cross-reactive antibody responses to 2009 H1N1 in these groups renders them more susceptible to infection.

References

[1] Chowell G, Miller MA, Viboud C. Seasonal influenza in the United States, France, and Australia: transmission and prospects for control. *Epidemiol Infect 2008; 136:852-864.*

[2] Cowling BJ, Fang VJ, Riley S, Malik Peiris JS, Leung GM. Estimation of the serial interval of influenza. *Epidemiology 2009; 20:344-347.*

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