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

Purple Paper

Pandemic pH1N1 Weekly Literature Synthesis
(Week of December 6-12, 2009)

Dear Reader:
This issue of the *Purple Paper* is the last one of the year. The *Purple Paper* will resume in January 2010. Happy Holidays!
From all of us at NCCID

Effectiveness of Neuraminidase Inhibitors

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

The current systematic review is an **update of a 2005 Cochrane Review** that assessed the effects of neuraminidase inhibitors (NAIs – oseltamivir and zanamivir) in prophylactic and therapeutic use for mitigating influenza illness symptoms, the transmission of influenza, and complications from influenza in healthy adults. The Cochrane group, led by Dr. Tom Jefferson, was responding to a query about the validity of inclusion of unpublished data from clinical trials sponsored by F. Hoffmann-La Roche Ltd., the maker of Tamiflu®, that ultimately led the 2005 review to conclude oseltamivir is effective in reducing important complications of influenza. Having attempted, but failing, to obtain raw data from Roche, the authors of this updated Cochrane Review excluded such previously unpublished studies. The authors updated a search of the Cochrane central register of controlled trials (*Cochrane Library 2009, issue 2*), which contains the Acute Respiratory Infections Group's specialized register, Medline (1950-Aug 2009), Embase (1980-Aug 2009). The group also carried out an additional search for evidence of harms, including submitting a Freedom of Information Act request to the US Food and Drug Administration for all data on the harms of oseltamivir and zanamivir (i.e. pharmacovigilance data). Only randomized studies that compared oseltamivir or zanamivir in otherwise healthy people exposed to naturally occurring influenza, against placebo, control anti-virals, or no intervention with outcomes of influenza (efficacy) or ILI (effectiveness) were included. Of the 20 trials included for analysis, 4 were on prophylaxis, 12 on treatment, and 4 on post-exposure prophylaxis.

For prophylaxis, evidence was insufficient to support or refute the effect of NAIs on ILI or asymptomatic influenza. Compared with placebo, the efficacy of prophylactic use of oseltamivir against laboratory-confirmed influenza was 61% and 73% for a daily dosage of 75mg and 150mg; and zanamivir was 62% efficacious at a daily dosage of 10mg. Oseltamivir had an efficacy of 58% and 84% in two household trials for post-exposure prophylaxis; two zanamivir trials reported similar results (80% and 81%). Hazard ratios for oseltamivir and zanamivir treatment of symptomatic influenza were 1.20 and 1.24, respectively, suggesting that anti-viral treatments can shorten the duration of influenza illness when administered within 48 hours of the onset of symptoms. After exclusion of unpublished studies on influenza-associated complications (pneumonia, bronchitis, other lower respiratory tract infections, otitis media, sinusitis), the remaining data showed no benefit for oseltamivir against complications.

In terms of harms, trial evidence indicated that oseltamivir induces nausea, especially at the higher daily dosage of 150mg. Furthermore, retrospective comparative safety data on oseltamivir suggested an incidence of 20-27 and 30-40 neuropsychiatric adverse events per 1000 adults aged 18-49 at 14 days and 30 days, respectively. In prospective clinical trials, the incidence of neuropsychiatric adverse events as a result of oseltamivir treatment was 0.5%. No statistically significant adverse event was found for zanamivir.

Overall, NAIs have modest effectiveness against the symptoms of influenza in otherwise healthy adults. The summary below is reproduced from the current Cochrane paper. It is included here to highlight some outstanding issues related to the effects of NAIs on influenza.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- NAIs (especially oseltamivir) have become global public health drugs for influenza.
- They prevent symptoms and shorten the duration of illness by about one day if taken within 48 hours of the onset of symptoms.
- Toxicity and the effects on complications have been debated.

WHAT THIS STUDY ADDS

- NAIs reduce the symptoms of influenza modestly.
- NAIs reduce the chance of people exposed to influenza developing laboratory-confirmed influenza but not ILI.
- Evidence for or against their benefit for preventing complications of influenza is insufficient.
- Evidence for or against serious adverse events is lacking, although oseltamivir causes nausea.

Epidemiology of pH1N1

Estimates of the prevalence of pandemic (H1N1) 2009, United States, April-July 2009.
Reed C et al. *Emerg Infect Dis 2009; 15:2004-2007.*

Between April-July 2009 during the first wave of the pandemic, a total of 43,677 laboratory-confirmed pH1N1 cases were reported in **the USA**. Since not all pH1N1 cases were reported and laboratory-confirmed, this figure likely represents a substantial underestimate. To generate a figure that more closely approximates the actual number of cases during the same period, CDC investigators designed a simple step-wise multiplier model that takes into account the proportion of people who would proceed through a linear identification process from becoming infected to laboratory confirmation. The steps in this linear identification process are:

1. Total number of pH1N1 cases
2. Proportion of pH1N1cases who sought care for illness
3. Proportion of pH1N1 cases who had specimen collected
4. Proportion of pH1N1 cases whose specimen was tested for influenza
5. Proportion of pH1N1 cases whose specimen was positive for pH1N1
6. Proportion of pH1N1 cases who were tested positive and reported

At each step, a range of proportions was derived from pH1N1 outbreak investigations, prior studies and surveys, including the 2007 Behavioural Risk Factor Surveillance Survey (BRFSS).

Since it is known that 43,677 laboratory-confirmed pH1N1 cases were identified (Step 6), one can work backwards to determine the total number of people who were initially infected with pH1N1 (Step 1). Via this approximation process, the investigators estimated that every reported pH1N1 case may represent 79 total cases. This translates to a median estimate of 3 million total symptomatic pH1N1 cases (range 1.8-5.7 million).

Using a similar approximation method, it was estimated that every hospitalized pH1N1 case may represent a median of 2.7 total hospitalized cases. The reported figure of 5,009 hospitalized pH1N1 cases translates to a median estimate of 14,000 hospitalizations (range 9,000-21,000). Applying the ratio of death to hospitalization of 6%, there was a median estimate of 800 deaths (range 550-1,300) as a result of pH1N1 infection in the USA.

Respiratory infection in institutions during early stages of pandemic (H1N1) 2009, Canada.
Marchand-Austin A et al. *Emerg Infect Dis 2009; 15:2001-2003.*

During the first wave of the 2009 influenza pandemic, reporting of respiratory outbreaks in institutions across **Ontario** continued as required by law. To examine how the emergence of pH1N1 affected the incidence of respiratory outbreaks in institutions, investigators from PHAC and Ontario Agency for Health Protection and Promotion reviewed respiratory outbreaks registered with the Public Health Laboratory during early stages of the pandemic between April 20 and June 12, 2009.

Of the 83 respiratory outbreaks submitted for laboratory testing, of which 77 occurred in long-term care facilities (LTCFs), only 2 were associated with pH1N1. The first pH1N1 outbreak occurred in a LTCF on June 3. The second took place on June 11 in a hospital treating patients with ILI. The majority of the remaining respiratory outbreaks were caused by enterovirus/rhinovirus, followed by

parainfluenza 3, metapneumovirus, and influenza A/H3N2.

Despite widespread community prevalence, only one pH1N1-related outbreak was identified in a LTCF. This suggests that residents of LTCFs may have pre-existing immunity against pH1N1, or were relatively isolated from people of younger age groups who had travelled to risk areas.

pH1N1 in Vulnerable Populations

Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives – 12 States, 2009.
CDC. *MMWR 2009 Dec 11; 58:1341-1344.*

Twelve states, which together represent 50% of the American Indian/Alaska Natives (AI/AN) population in **the USA,** participated in a CDC-led workgroup that assessed the burden of pH1N1 deaths in aboriginal peoples. Compiled surveillance data collected between April 15, 2009 and November 13, 2009 were analyzed in conjunction with review of death certificates, medical records, or death investigation reports to determine the race/ethnicity and influenza risk status of those who succumbed to pH1N1 disease.

A total of 426 pH1N1-associated deaths were reported by the 12 states during the study period. Although AI/AN only make up approximately 3% of the total population of the 12 states, they accounted for 10% of reported pH1N1 deaths. The overall AI/AN pH1N1-related death rate of 3.7/100,000 population was 4x higher than persons in all other racial/ethnic populations combined (pH1N1 death rate = 0.9/100,000).

Furthermore, a higher proportion of AI/AN had high-risk health conditions compared to persons in all other racial/ethnic populations combined. The incidence of diabetes and asthmas was 2x higher among AI/AN decedents (45.2% and 31.0%) than decedents in all other racial/ethnic populations combined (24.0% and 14.1%).

NCCID Comments:
In Canada, Aboriginal peoples account for 3% of the national population; however, they are over-represented among those who were hospitalized, admitted to ICU or had succumbed to pH1N1 disease. This may be due to the fact that Aboriginal communities have more pregnant women, younger children, and underlying medical conditions than the general Canadian population.

Since the beginning of the pandemic in April 2009 to August 29, 2009 (the official end of the 2008/09 seasonal influenza season in Canada), 241 (16.6%) hospitalized pH1N1 cases were Aboriginal (148 First Nations, 74 Inuit, 18 Métis, and 1 ethnicity unknown) [1]. Cases among all Inuit, compared to First Nations population, had 7x higher hospitalization rates (146.6 vs. 21.2 per 100,000 population) and 7x higher mortality rates (4.0 vs. 0.6 per 100,000). However, hospitalized cases of Inuit ethnicity were younger (median age 4 vs. 18), admitted to ICU less frequently (11.3% vs. 21.6%) and had fewer underlying medical conditions (17.6% vs. 62.7%) than their counterparts of First Nations ethnicity [1].

According to the latest FluWatch report [2], among all hospitalized pH1N1 cases reported between August 30, 2009 and December 5, 2009 during the second wave of the pandemic, 232 (4.0%) cases were among Aboriginal peoples. Although the hospitalization rate among Aboriginal peoples appeared to be lower in the second wave compared to the first wave, rates of ICU admissions and mortality were slightly higher.

Oseltamivir-Resistant Seasonal Influenza

Emergence of H274Y oseltamivir-resistant A(H1N1) influenza viruses in Japan during the 2008-2009 season.
Baranovich T et al. *J Clin Virol. Published online December 3, 2009.*

To assess the emergence of oseltamivir-resistant seasonal influenza A/H1N1 viruses in **Japan**, the investigators isolated seasonal A/H1N1 viruses from respiratory samples collected from influenza patients between December 2007 and April 2008 (2007/08 season) and between December 2008 and April 2009 (2008/09 season) in 7 prefectures through a physician-based sentinel surveillance system. Oseltamivir resistance was determined by laboratory assays. None of the patients received amantadine, oseltamivir or zanamivir before testing for influenza.

Of a total of 773 and 1364 influenza viruses isolated during the 2007/08 and 2008/09 seasons, 687 (89%) and 745 (55%) were of the seasonal A/H1N1 subtype, respectively. Three of the 687 (0.4%) 2007/08 seasonal A/H1N1 isolates and all of the 745 (100%) 2008/09 seasonal A/H1N1 isolates had the H274Y mutation (a change from histidine to tyrosine in amino acid position 274) in neuraminidase (NA), conferring oseltamivir resistance. Oseltamivir-resistant seasonal A/H1N1 viruses with the H274Y mutation showed a 300-400x reduction in susceptibility to oseltamivir compared to seasonal A/H1N1 viruses without the H274Y mutation. Amantadine resistance, which is characterized by the S31N mutation (a change from serine to asparagine in amino acid position 31) in the M2 protein, was detected in 431 of the 687 (62.7%) of the 2007/08 seasonal A/H1N1 isolates but in none of the 2008/09 seasonal A/H1N1 isolates. None of the seasonal A/H1N1 isolates from both seasons demonstrated reduced susceptibility to zanamivir.

The investigators also attempted to characterize the "temporal-familial" relationship between the 2007/08 and 2008/09 seasonal A/H1N1 isolates by studying their genetic sequences in comparison to sequences of other reference A/H1N1 strains (i.e. WHO recommended A/H1N1 vaccine strains and other known oseltamivir-resistant and -sensitive A/H1N1 strains). They found that the Japanese seasonal A/H1N1 isolates separated into 2 clades: 2C and 2B. Clade 2C included primarily amantadine-resistant and oseltamivir-sensitive 2007/08 seasonal A/H1N1 viruses. Clade 2B was further divided into subclades 2B.I and 2B.II. Except for two Japanese 2007/08 seasonal A/H1N1 isolates that were amantadine-sensitive and oseltamivir-resistant, the majority of Japanese A/H1N1 viruses belonging to subclade 2B.I were amantadine- and oseltamivir-sensitive. All seasonal A/H1N1 isolates belonging to subclade 2B.II were amantadine-sensitive and oseltamivir-resistant. In addition to the H274Y mutation in NA, all subclade 2B.II viruses possessed a D375G mutation (a change from aspartic acid to glycine in amino acid position 375) in NA and an A193T mutation (a change from alanine to threonine in amino acid position 193) in hemagglutinin (HA).

NCCID Comments:
This study demonstrated that oseltamivir-resistant 2008/09 seasonal influenza A/H1N1 viruses were substantially less susceptible to oseltamivir in laboratory assays than sensitive viruses, but remained zanamivir-sensitive. This finding is congruent with the observation that patients who were treated with oseltamivir despite being unknowingly infected with oseltamivir-resistant 2008/09 influenza A/H1N1 viruses, had significantly longer fever episodes than their counterparts receiving zanamivir [3] (See the 3rd issue of the *Purple Paper*).

The A193T mutation detected in HA of 2008/09 seasonal influenza A/H1N1 viruses is of interest. Since oseltamivir specifically inhibits the function of NA, the A193T mutation in HA did not appear to have arisen due to direct selective pressure from oseltamivir. Interestingly, the same mutation is also found in amantadine-resistant seasonal influenza A/H1N1 viruses isolated in Japan during the 2006/07 season [4]. The driving forces behind the emergence of the A193T mutation and its significance are currently unclear. Further research is needed to address these issues.

pH1N1 as Urban Public Health Crisis

Pandemic influenza as 21st century urban public health crisis.
Bell DM et al. *Emerg Infect Dis 2009; 15:1963-1969.*

This **policy review** paper revisits public health mitigation measures that were implemented in **Mexico City** and **New York City** (NYC) in response to the emerging pH1N1 pandemic during spring 2009. It identifies commonalities between the emergency preparedness plans activated in the two megacities and highlights challenges that have arisen.

Mexico City
National surveillance detected an atypically high incidence in ILI in mid-to-late February 2009 that further increased in early-to-mid April. Active surveillance in 23 hospitals in Mexico City led to the reporting of previously healthy young adults with severe pneumonia. The causative agent was later identified to be a novel influenza A/H1N1 virus on April 23. On April 24, the federal government

activated the national pandemic influenza preparedness plan and coordinated community mitigation measures in Mexico City and the neighbouring state with participation of state authorities. The Mexican pandemic mitigation strategy involves the following core elements:

1. With cooperation of the private sector, an intensive, multi-faceted mass media campaign was launched to inform the general public about influenza. A call centre was assembled by a Mexican telephone company that received >5 million calls. Health messages from the Ministry of Health were available as traditional print materials, and electronic materials that were disseminated through text messaging and mass emails.
2. Personal hygiene was promoted. Salutatory kissing and hugging were discouraged. Frequent hand washing and cough etiquette were encouraged. Alcohol-based hand sanitizers were made available in all government and private facilities open to the public. Alcohol-based hand sanitizers were also provided in areas or households where there is a limited water supply. Disposable surgical masks were distributed to the general population by military personnel.
3. Extensive social distancing measures were implemented. Blanket school closures began on April 24 in Mexico City and nationwide soon after. All schools were thoroughly cleaned before reopening on May 11. Children were screened for fever and respiratory symptoms everyday upon arrival at school. Ill children were sent home and could only return to school with a written note from their primary healthcare provider granting medical clearance. Public spaces and events that could draw large crowds were closed. Dine-in services in all restaurants were suspended. Movie theatres were closed. Live audience attendance was prohibited at large sports events, churches and temples; sports matches and religious services were broadcast over radio and television instead. Grocery stores and supermarkets remained open, but with additional cashiers to keep lines short. Mass transit systems operated normally. Masks were provided to drivers and passengers. Mass transit vehicles were cleaned frequently. Thousands of workplaces in Mexico City and the rest of country were closed for several days.
4. Sick persons with ILI were encouraged to seek prompt medical care and requested to stay home to recover. The national anti-viral stockpile was released by the federal government, and distributed to ill persons and their close contacts free of charge.

New York City

As a result of the World Trade Centre and anthrax attacks in 2001, and in anticipation of an influenza pandemic, emergency preparedness planning in NYC was emphasized and accelerated. The first case of pH1N1was introduced in a school that eventually led to a city-wide outbreak. The NYC pandemic mitigation strategy involves the following core elements:

1. Novel syndromic surveillance systems were put in place during the preparedness phase to monitor visits to hospital emergency departments, calls to emergency medical services, pharmacy sales, worker absenteeism, and outpatient clinic visits. These systems were activated for real-time tracking of the pandemic in NYC during the first wave. Systems for collecting etiological information from virological studies on samples of outpatients and hospitalized patients with ILI were also implemented.
2. An extensive public communications campaign was implemented through a pre-existing program of the NYC Office of Emergency Preparedness. Health messages were translated into many languages for outreach to ethnic populations. Frequent press conferences in English and Spanish were held by the NYC mayor and health commissioner. The NYC government established an information hotline that operated 24 hours a day, 7 days a week with live operators. A separate electronic health alert network was made available to healthcare providers for conveyance of health messages.
3. Community mitigation measures focused on selective closures of schools. Household contacts of pH1N1 cases were not quarantined. Businesses were not closed. Public gatherings were not cancelled. Reactive school closures were decided on an individual basis, depending on the number of visits of ILI to the school nurse

and other factors, such as the ability of students to comply with respiratory hygiene. Approximately 50 schools were closed for 1 week during the spring wave of the pandemic.

4. Medical interventions were also integral to the NYC pandemic mitigation strategy. An anti-viral emergency stockpile was available for dispatch, but the need to use it did not arise as normal distribution channels sufficed. If the stockpile had been needed, anti-virals would have been distributed to community health centres, public clinics and hospitals. Vaccines were prioritized for high-risk populations, depending on indications for use, availability, and urgency of administration. Mass vaccination clinics were held at 200 sites across the city.

There are shared elements in both pandemic mitigation plans of Mexico City and NYC. Robust, comprehensive communications and outreach to disadvantaged persons were major themes. Anti-virals were stockpiled for both prophylactic and therapeutic use. The feasibility of various social distancing measures largely depended on and must be tailored to local situations.

The experience of Mexico City and NYC also highlighted some important issues that need to be addressed for future emergencies:

1. Not only does an effective emergency response hinge on effective coordination between all governmental levels that may span several geographic jurisdictions, it also requires the collaboration of public health and emergency management agencies, and cooperation from the private and other non-governmental sectors. Coordination with the private and other non-governmental sectors should be better defined and more formally established.
2. Surveillance and monitoring of illness trends is a continuing challenge, and this is even more so for cities that do not have the human/material resources and technical expertise. Illness surveillance primarily depends on the organization and provision of health services, therefore cities with universal health coverage will have apparent advantages. Surveillance in some cities is also complicated by persons who do not have fixed addresses or who live in slums. The lack of laboratory capacity for detection and identification of a new emerging pathogen poses further challenges in many cities.
3. Disease containment and mitigation measures that involve alteration of social behaviours and interactions are difficult to implement, and their effectiveness difficult to assess. School closures as a mitigation intervention are problematic. The objectives of school closures (i.e. to protect high-risk students, all students, families; to slow community transmission) during a less severe pandemic are often unclear. The effectiveness of school closure is difficult to quantify, given that such measures do not prevent students from congregating elsewhere when schools are closed. School closures may also cause considerable societal disruptions. Many questions remain regarding implementation of social distancing and infection control measures in institutions (e.g. healthcare institutions, universities/colleges, workplaces) and public spaces with substantial people flow (e.g. mass transit, airports).
4. Timely delivery and administration of vaccines and anti-virals to persons who need them are key to prevention and treatment of pH1N1. This task is not easy for persons with known, fixed addresses, and it is even more difficult when the targeted persons are elderly, homebound, undocumented, homeless, live in slums or are transient residents. Enhanced targeted strategies may require innovative solutions.
5. An effective communications strategy is a reciprocal process between the communicator and audience. It must build and maintain trust, ensure transparency, announce information in a timely manner, and be receptive to the public's queries and concerns. Preparatory planning is important. As demonstrated by the communications campaigns in Mexico City and NYC, in addition to traditional mass media and the Internet, transmitting health or emergency messages through cell phone networks (i.e. via text messaging and other social networking tools such as Twitter©) can ensure dissemination to a broad audience. This communications model may have great potential for developing countries where mobile phones are commonly available, but computer/internet access is limited.

Economic Benefits of Mitigation Strategies

The macroeconomic impact of pandemic influenza: estimates from models of the United Kingdom, France, Belgium and the Netherlands.
Keogh-Brown MR et al. *Eur J Health Econ. Published online December 9, 2009.*

In this **simulation model** based on single-country economies, the potential economic impact of pandemic influenza, school closures, prophylactic absenteeism (absence from work in the attempt to avoid infection), anti-viral and vaccination strategies was assessed for **the UK, France, Belgium and the Netherlands**. The potential economic impact of various mitigation strategies was estimated as the % loss of gross domestic product (GDP) and simulated for mild and severe influenza disease scenarios.

In both mild and severe influenza disease scenarios for all 4 countries, school closures (for 4 or 13 weeks) and prophylactic absenteeism (for 1 or 4 weeks) cause an increased % GDP loss vs. no mitigations. Compared to no mitigation, vaccination could result in larger savings than anti-viral treatment for both mild and severe disease scenarios. A combined anti-viral and vaccination strategy has a synergistic effect in reducing % loss of GDP. Applying this model to the UK, the savings translate to £4.1bn, £5.7bn and £8.0bn, respectively, for the anti-viral, vaccination and combined strategy in a mild pandemic, and £20.2bn, £25.3bn and £33.3bn in a severe pandemic. The approximate cost of the anti-viral and vaccination strategies had been estimated to be £0.75bn and £0.85bn. Therefore, in addition to health benefits afforded by these interventions, the consequent substantial savings also means that anti-viral and vaccination strategies would be worthwhile from the economic perspective.

The findings here are consistent with results of another British study that utilized similar modelling parameters to estimate the economic impact of a pandemic [5] (see the 2nd issue of the *Purple Paper*).

Notable Publications

Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation.
Burch J et al. *Health Technol Assess 2009; 13:1-290.*

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[2] Public Health Agency of Canada. FluWatch: November 29, 2009 to December 5, 2009 (Week 48). Available online: http://www.phac-aspc.gc.ca/fluwatch/09-10/w48_09/index-eng.php

[3] Kawai N et al. Clinical effectiveness of oseltamivir and zanamivir for treatment of influenza A virus subtype H1N1 with the H274Y mutation: a Japanese, multicenter study of the 2007-2008 and 2008-2009 influenza seasons. *Clin Infect Dis 2009; 49:1828-1835.*

[4] Saito R et al. Increased incidence of amantadine-resistant influenza A(H1N1) and A(H3N2) viruses during the 2006-2007 influenza season in Japan. *J Infect Dis 2008; 197:630-632.*

[5] Smith RD et al. The economic-wide impact of pandemic influenza on the UK: a computable general equilibrium modelling experiment. *BMJ 2009; 339:b4571.*

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