National Collaborating Centre for Infectious Diseases
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Purple Paper

Pandemic pH1N1 Weekly Literature Synthesis
(Week of January 10-16, 2010)

Mitigation Strategy Simulation Modelling

When should we intervene to control the 2009 influenza A(H1N1) pandemic?
Sato H et al. *Euro Surveill. 2010;15(1):pii=19455.* Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19455

From April 28-June 18, 2009, the Ministry of Health, Labour and Welfare of Japan imposed onboard quarantine inspections at major international airports in an attempt to delay import of pH1N1 from overseas. At Narita International Airport, the largest international airport in Japan, > 2 million travellers from North America were screened; 10 cases of pH1N1 were detected by laboratory tests and 60 contacts were quarantined.

Using **mathematical simulation modelling**, the investigators estimated the number of imported pH1N1 cases among flight passengers, who might have entered Japan undetected despite onboard quarantine inspections. This approximation was based on several variables: the number of detected cases, the duration of incubation and the duration of infectious periods.

In addition, the investigators attempted to determine the optimal timing for implementing public health interventions during the early phase of the first pandemic wave. The simulation model assumed that a proportion of symptomatic pH1N1 cases would be detected and isolated at border quarantine, while a proportion of cases would enter the country undetected and transmit the virus to a susceptible indigenous population of 100,000 individuals. Public health interventions were introduced (in the model) on Day 1, 6, 11 and 16 after the first pH1N1 case was detected at the border quarantine. The effectiveness of intervention initiated at each time variable was compared to no intervention in terms of the reduction of the rate of maximum number of cases per day. An intervention is any non-pharmaceutical action that reduced exposure to infectious cases and included school closure and government-ordered home isolation. There were three levels of compliance to a public health intervention (i.e. home confinement as a result of school closure and government-ordered home isolation): low (10%), intermediate (30%) and high (50%). Homebound susceptible individuals abstained from contact with infectious individuals for a duration of 3, 7, or 14 days. For this second exercise, incubation and infectious periods were both set at 3.5 days and the reproduction number was set at 2.3. These pH1N1 epidemiological parameters were derived from published literature.

In this simulation study, border quarantine inspection would have detected the first case of H1N1 influenza in Japan in 56 days after the reported first case in Mexico. By this time, more than 100 cases would have already entered the country. The detection rate of border quarantine inspection was estimated to be between 7.1% and 22.3%. Therefore, onboard quarantine inspection does not appear to be an effective public health intervention in preventing import of pH1N1.

Public health interventions of low compliance (10%) would have been minimally effective in reducing the maximum number of daily symptomatic cases and delaying the epidemic peak, regardless of the start date and duration of the intervention. For public health interventions of intermediate (30%) and high (50%) level of compliance, implementation on day 6 after the identification of the first case in Japan, for a duration of 14 days, would have been most effective in reducing the maximum number of cases per day (by 44% and 36%, respectively) and delaying the epidemic peak (by 17 and 9 days, respectively). Introduction of interventions on day 1 would not have achieved the best outcome.

Optimal Pandemic Influenza Vaccine Allocation Strategies for the Canadian Population.
Tuite A et al. *PLoS Currents: Influenza. 2010 Jan 4:RRN1144.*

This study was published in the open-access, internet-based journal, Public Library of Science (PLoS) Currents: Influenza*, that is aimed at rapid exchange of scientific findings and ideas regarding pH1N1. Content presented in this journal does not undergo in-depth peer-review in the interest of time, but is moderated by an expert panel of influenza researchers.*

In this **mathematical modelling** study, the investigators determined the effect of different vaccination strategies on severe outcomes of pH1N1 infection. The primary outcome measures were attack rates, hospitalizations, intensive care unit (ICU) admissions, and mortality.

The model ran from mid-April, 2009 (the date of the identification of the first laboratory-confirmed pH1N1 case in Ontario) to June 30, 2010, representing a single influenza season. Epidemiological parameters were based on surveillance data from Ontario. The reproduction number was 1.3 (range 1.15-1.31). The latent period was set at 3.5 days and duration of infectiousness at 2.5 days.

The test population of 31,612,905 individuals was compartmentalized into 4 different disease states:
- Susceptible
- Exposed (infected but not infectious)
- Infectious
- Recovered and immune.

The test population was also divided into 7 age classes. Each age class was assigned a unique set of characteristics:
- Demographic information
- Proportion with underlying high-risk conditions (one or more of: asthma, emphysema, chronic obstructive pulmonary disease, diabetes, heart disease, cancer, stroke)
- Proportion who are pregnant
- Hospitalization rate
- ICU admission rate
- Case-fatality rate.

These age-group specific characteristics were derived from surveillance data of all laboratory-confirmed pH1N1 cases in Ontario from April 13-June 21, 2009, health surveys, the 2006 Canadian Census and published literature.

Transmission of pH1N1 took place via contact between infectious and susceptible individuals in non-homogenous mixing patterns within and among age groups. The model assumed 40% of infections were asymptomatic, but did not take into account differential transmission of pH1N1 by symptomatic and asymptomatic cases.

Two doses of pH1N1 vaccine (the first dose given on November 15, 2009 and the second dose 21 days later) were modelled. Pandemic H1N1 vaccine effectiveness was set at 70%. The 4 main vaccination allocation strategies under examination were:
1. Attack rate-based strategy: Vaccine was administered first to age groups with the highest model-predicted attack rate.
2. Outcome-based strategy: Vaccine was administered first to age groups with the highest risk of severe outcome (hospitalization, ICU admission or death) as a result of pH1N1 infection.
3. Risk-based strategy and subsequent *attack rate*-based strategy: Vaccine was first administered to individuals of any age who are at increased risk of pH1N1-complications due to underlying medical conditions and/or pregnancy (in the second and third trimester). This is followed by the implementation of an *attack rate*-based strategy as above.
4. Risk-based strategy and subsequent *outcome*-based strategy: Vaccine was first administered to at-risk individuals as #3 above, followed by the implementation of an *outcome*-based strategy.

Each vaccination allocation strategy was tested under different conditions:
1. Pre-existing immunity – each vaccination strategy was tested with the assumption that 30%, 50% or 70% of individuals aged ≥53 years had pre-existing immunity against pH1N1.
2. Vaccination coverage of each age class – a base coverage of approximately 30% and an upper bound of approximately 60% for most age groups were modelled.

3. Timing of the epidemic peak – epidemic peaks occurring in October, November, December, 2009 and January 2010 were modelled.

According to the results of this model, the average pH1N1 attack rate across the entire Canadian population would be 35.1% (range 33.2%-36.8%) in the absence of vaccination.

In general, both attack rate-based and outcome-based vaccination allocation strategies showed variable levels of effectiveness in reducing attack rates, hospitalizations, ICU admissions and mortality depending on the combination of the timing of the pH1N1 epidemic peak, pre-existing immunity and vaccination coverage. Compared to either attack rate-based or outcome-based strategy alone, the two-tier approach achieved a more substantial reduction in hospitalizations and ICU admissions. This was true for all scenarios of pre-existing immunity, vaccination coverage and epidemic peak. However, the two-tier strategy only had a moderate effect in reducing mortality. In fact, when the epidemic peak occurred in December or January, the two-tier approach had no effect in reducing mortality compared to either attack rate-based or outcome-based strategy alone. Moreover, it should be noted that benefits of the two-tier strategy in improving severe pH1N1-associated outcomes were achieved at a cost of increased higher population-level attack rates for all scenarios.

As recent data suggest one vaccine dose is efficacious in inducing protective immunity against pH1N1, the investigators also tested the impact of one vaccine dose on the measured outcomes. They found no difference in the rank-order of the vaccination strategies for most scenarios. However, if the epidemic peak occurred in January 2010 and high vaccination coverage could be achieved, the attack rate-strategy would be preferred to the outcome-based approach for all outcomes. In other words, the attack rate-strategy for distributing one vaccine dose would only be effective when the vaccine is available well in advance of the epidemic peak.

As the authors note, there were limitations to this mathematical model:

1. There was uncertainty regarding the model epidemiological parameters of pH1N1 that were primarily based on surveillance data from Ontario, although these appeared to be in agreement with estimates derived from other settings.
2. The study did not account for spatial heterogeneity in the interaction within and among age groups.
3. Differential transmission of pH1N1 by symptomatic and asymptomatic cases was not considered.
4. The effect of other public health mitigation strategies (e.g. anti-virals and social distancing measures) on pH1N1 transmission and associated outcomes was not evaluated.
5. The effect of co-circulating seasonal influenza viruses on the transmission of pH1N1 was not taken into consideration; nonetheless, only few seasonal influenza A and B isolates have been identified since the beginning of the pandemic. According to the latest *FluWatch –January 10 to 16, 2010 (Week 2)*, pH1N1 accounted for >99.8% of all positive influenza A subtyped specimens from August 30, 2009 to January 16, 2010 [1].

NCCID Comments:
In many provinces, pandemic vaccination clinics began on October 26, 2009. Due to a shortage of pH1N1 vaccines, priority groups recommended to receive the vaccine included:

- People with chronic medical conditions >65 years of age
- Pregnant women
- Children aged 6 months to >5 years
- People living in remote and isolated settings or communities
- Health-care workers involved in pandemic response or who deliver essential health services
- Household contacts and caregivers of individuals who are at high risk, and who cannot be immunized (such as infants under six months of age or people with weakened immune systems).

Hence, according to this model, vaccinating first individuals who had underlying conditions or who were pregnant, followed by the wider public, may have reduced considerably the number of hospitalizations, ICU admissions and deaths.

Seasonal Influenza Vaccine Allocation in the Canadian Population during a Pandemic.
Tuite A et al. *PLoS Currents: Influenza. 2010 Jan 4:RRN1143.*

This study was published in the open-access, internet-based journal, PLoS Currents: Influenza*, that is aimed at rapid exchange of scientific findings and ideas regarding pH1N1. Content presented in this journal does not undergo in-depth peer-review in the interest of time, but is moderated by an expert panel of influenza researchers.*

An unpublished Canadian study surfaced in early September 2009 suggesting receipt of seasonal influenza vaccine may increase the risk of pH1N1-associated illness. To investigate how the potential increased pH1N1 risk might affect the reduced influenza-associated mortality conferred by seasonal influenza vaccination, the authors of this study develop a **mathematical model** to examine different seasonal influenza vaccination strategies during a pandemic period with co-circulation of various proportions of both pH1N1 and seasonal influenza.

The study was authored by the same investigators of the previous paper. Thus, many of the model parameters and data sources from which assumptions were drawn were the same as above:

- The model ran from mid-April, 2009 to June 30, 2010, representing a single influenza season.
- The test population of 31,612,905 individuals was compartmentalized in 4 different disease states and divided into 7 age classes.
- Each age class was assigned demographic information based on the 2006 Canadian Census.
- Transmission of pH1N1 took place via contact between infectious and susceptible individuals in non-homogenous mixing patterns within and among age groups. 40% of infections were asymptomatic.
- Epidemiological parameters for pH1N1 used in this model were the same as above.

Parameters unique to this model were:

- The three seasonal influenza A and B strains were represented as a single strain in this model (to reduce model complexity).
- Individuals who were immune to one strain of influenza (as a result of infection or vaccination) remained susceptible to the second strain.
- Each age class was assigned a set of characteristics relating to the proportion with pre-existing immunity, vaccine coverage and case fatality that were specific to pH1N1 and seasonal influenza.
- Model epidemiological parameters for seasonal influenza were based on estimates from published literature. The reproduction number ranged from 1.3-1.4. The latent period was set at 2.1 days and duration of infectiousness at 4.8 days.
- Vaccination was considered to occur simultaneously across the population. Immunity developed 2 weeks after vaccination.
- Vaccine effectiveness was 70% in individuals aged 0-64 years and 50% in individuals aged ≥65 years. These parameters were used for both pH1N1 and seasonal influenza vaccines.
- For all scenarios, a single dose of the pH1N1 vaccine was administered in mid-November.
- It was assumed that the receipt of seasonal influenza vaccine in susceptible individuals was the only way whereby risk to pH1N1 could be enhanced.
- The outcome measured in this model was the total influenza-attributable mortality.

The 4 seasonal influenza vaccination strategies under examination were:

1. No seasonal vaccination
2. Seasonal vaccination in early October 2009
3. Seasonal vaccination in early January 2010
4. Seasonal vaccination of individuals aged ≥65 years in early October followed by vaccination of individuals aged <65 years in early January.

For seasonal vaccination strategies in early October 2009 and early January 2010, both vaccination of the entire population and vaccination of individuals aged ≥65 years were evaluated.

The effect of each seasonal influenza vaccination strategy on total influenza-attributable mortality was examined under different conditions:

1. Timing of the pH1N1 epidemic peak – epidemic peak occurring in either mid-November 2009 or mid-January 2010 was modelled.

2. Seasonal vaccine-associated relative risk – a range of relative risks (RR = 0.9-2.0) of pH1N1 following seasonal influenza vaccination was modelled.
3. Different proportions of co-circulating seasonal influenza were modelled: 1.8% (where R_0 was equivalent to 1.3), 6.2% (R_0=1.35), and 16.2% (R_0=1.4). The pH1N1 virus made up the remaining proportions of circulating influenza strains.

1) No seasonal vaccination

According to this model, when only the pH1N1 vaccine was administered in mid-November in the absence of any seasonal vaccination program, total influenza-attributable mortality would increase as the proportion of circulating seasonal influenza increased. The overall mortality would be greater for the pH1N1 epidemic peak in November 2009 than in January 2010. Since this model assumed that pH1N1 vaccine was administered in mid-November, there would not have been enough time for the development of protective immunity against pH1N1 for a November 2009 peak.

2) Seasonal vaccination in early October 2009

For a pH1N1 epidemic peak in November 2009, when seasonal influenza vaccine was administered to all age groups at low (1.8%) and intermediate (6.2%) levels of circulating seasonal influenza, the total number of deaths was higher than in the absence of vaccination. This effect was evident when the relative risk of pH1N1 associated with seasonal influenza vaccine receipt exceeded 1.1 and 1.4 respectively. However, targeting seasonal vaccination to individuals aged ≥65 years would be more effective at reducing the total number of deaths, albeit more so at intermediate levels of circulating seasonal influenza than at low levels. In the presence of low levels of circulating seasonal influenza, the "no seasonal vaccination" strategy would be preferred once the vaccine-associated relative risk of pH1N1 surpassed 1.2, as the total number of influenza deaths began to rise and no benefits could be had from elderly-targeted seasonal vaccination at this point.

For a pH1N1 epidemic peak in January 2010, similar results were observed, but a higher vaccine associated-relative risk of pH1N1 was tolerated before the "no seasonal vaccination" approach would be preferred.

In the presence of high (16.2%) levels of circulating seasonal influenza, seasonal influenza vaccination of the entire population or individuals aged ≥65 years could reduce the total number of deaths for all combinations of pH1N1 epidemic peak and seasonal vaccine-associated relative risk of pH1N1.

3) Seasonal vaccination in early January 2010

For both pH1N1 epidemic peak in November 2009 or January 2010, delaying seasonal influenza vaccination to early January was more effective in reducing total influenza deaths compared to similar seasonal vaccination programs implemented in early October. In the presence of low levels of circulating seasonal influenza, targeting seasonal vaccination of individuals aged ≥65 years, rather than all age groups, could prevent more influenza deaths than the no vaccine approach regardless of the value of seasonal vaccine-associated relative risk of pH1N1.

In the presence of moderate and high levels of circulating seasonal influenza, both the population-wide and elderly-targeted seasonal vaccination strategies were effective in decreasing mortality compared to no vaccination, irrespective of pH1N1 epidemic peak and the seasonal vaccine-associated relative risk of pH1N1.

4) Two-stage vaccination approach

In this two-stage vaccination approach, seasonal influenza vaccination was first administered to individuals aged ≥65 years in early October 2009, followed by vaccination of the remaining age groups in early January 2010. For both pH1N1 epidemic peak in November 2009 or January 2010 and low levels of circulating seasonal influenza, the two-stage approach resulted in more deaths when the relative risk exceeded 1.4 compared to no vaccination.

At moderate and high levels of circulating seasonal influenza and for both pH1N1 epidemic peak in November 2009 or January 2010, the two-stage vaccination strategy was more effective in reducing influenza-related deaths than no vaccination.

NCCID Comments:
The original Canadian study suggesting that receipt of seasonal influenza vaccine is associated with an increased risk of pH1N1 illness that prompted the current modelling study is yet to be published. Since the findings are not supported by data from other countries (the US, UK, Australia and Mexico), the link between seasonal influenza vaccination and increased pH1N1 risk is speculative at this juncture. Therefore, assuming that there is no link (RR=1), this model projects that population-wide seasonal influenza vaccination in November 2009 would be the recommended strategy.

Nevertheless, given the uncertainty at the time, many public health jurisdictions had decided to delay seasonal influenza vaccination until after the pH1N1 epidemic peak in November. Thus, according to this model, seasonal influenza vaccination of all age groups in early January 2010 at low levels of circulating seasonal influenza would still prevent influenza-related deaths compared to no vaccination. However, the absolute number of deaths prevented in the national context would be relatively small.

pH1N1 in Vulnerable Populations

Quantifying the risk of pandemic influenza in pregnancy and Indigenous people in Australia in 2009.
Kelly H, Mercer GN, Cheng AC. *Euro Surveill. 2009;14(50):pii=19441.* Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19441

In this study, the investigators obtained surveillance data from May to October 2009 during the pH1N1 pandemic period in **Australia** and population data from the Australian Bureau of Statistics to estimate the burden of pH1N1 disease in pregnancy and people of indigenous status. Indigenous Australians, who identify themselves as Aboriginal or Torres Strait Islanders, account for approximately 2.5% of the Australian population. The investigators first estimated the cumulative incidence of hospitalization, ICU admission and death as a result of pH1N1 in the two vulnerable populations for the entire pandemic period. To calculate the relative risk, the investigators compared the cumulative incidence for each outcome in the vulnerable group with the same outcome in the entire population minus the estimated population of the vulnerable group.

A total of 4,833 hospitalizations, 650 ICU admissions and 186 deaths were reported as being attributable to pH1N1 between May and October 2009 during the pandemic period in Australia. These were equivalent to an incidence of 22.6, 3.0 and 0.9 per 100,000 population for hospitalization, ICU admission and death, respectively.

Among pregnant women, the incidence of hospitalization, admission to ICU and death were estimated to be 117.2, 19.8 and 1.3 per 100,000 population, respectively. Compared to non-pregnant women of reproductive age (15-44 years), pregnant women were at 5.2 times (range 4.6-5.8), 6.5 times (range 4.8-8.8) and 1.4 times (range 0.4-4.5) higher risk of hospitalization, ICU admission and death, respectively.

Among Indigenous Australians, the incidence of hospitalization, admission to ICU and death were estimated to be 150.3, 18.7 and 4.5 per 100,000 population, respectively. Compared to people of non-indigenous status, Indigenous Australians were at 6.6 times (range 6.2-7.2), 6.2 times (range 5.0-7.6) and 5.2 times (range 3.4-7.9) higher risk of hospitalization, ICU admission and death, respectively.

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 more 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), which roughly approximates the span of the first wave, 241 (16.6%) pH1N1 cases that required hospitalization were Aboriginal (148 First Nations, 74 Inuit, 18 Métis, and 1 ethnicity unknown) [2]. Cases among all Inuit, compared to First Nations population, had 7 times higher hospitalization rates (146.6 vs. 21.2

per 100,000 population) and 7 times 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 [2].

According to the latest *FluWatch* report, the proportion of Aboriginal peoples who experienced severe pH1N1 illness (hospitalizations, ICU admission and deaths) continued to be lower in the second wave compared to the first wave [1]. The proportions of Aboriginal peoples hospitalized, admitted to ICU and who succumbed to pH1N1 disease in the first wave were 20.2%-27.9%, 16.1%-21.8% and 11.5%-17.3%, respectively. The corresponding proportions in the second wave were 4.5%-5.6%, 6.0%-7.9% and 6.2%-8.8%. The cumulative proportions of Aboriginal peoples hospitalized, admitted to ICU and who died due to pH1N1 disease from April 12, 2009 to January 16, 2010 were 7.4%-9.3%, 8.0%-10.7% and 7.2%-10.3%, respectively. Furthermore, compared to the first wave, Aboriginal peoples hospitalized during the second wave have been older (median age 26 years vs. 12 years) and the proportion of cases with underlying medical conditions among Aboriginals was slightly higher (49.4% vs. 41.5%).

In a recent report by CDC investigators, a total 426 pH1N1-associated deaths were reported in American Indian/Alaska Natives (AI/AN) in 12 states between April 15, 2009 and November 13, 2009, whose AI/AN population represents 50% of all AI/AN in the USA [3]. Although AI/AN only make up approximately 3% of the total population of those 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 4 times higher than persons in all other racial/ethnic populations combined (pH1N1 death rate = 0.9/100,000).

References

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