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ORIGINAL ARTICLE

Observational Study

Pandemic influenza 2009: Impact of vaccination coverage on critical illness in children, a Canada and France observational study

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Abstract

AIM

To study the impact of vaccination critical illness due to H1N1pdm09, we compared the incidence and severity of H1N1pdm09 infection in Canada and France.

METHODS
We studied two national cohorts that included children with documented H1N1pdm09 infection, admitted to a pediatric intensive care unit (PICU) in Canada and in France between October 1, 2009 and January 31, 2010.

RESULTS
Vaccination coverage prior to admission to PICUs was higher in Canada than in France (21% *vs* 2% of children respectively, $P < 0.001$), and in both countries, vaccination coverage prior to admission of these critically ill patients was substantially lower than in the general pediatric population ($P < 0.001$). In Canada, 160 children (incidence = 2.6/100000 children) were hospitalized in PICU compared to 125 children (incidence = 1.1/100000) in France ($P < 0.001$). Mortality rates were similar in Canada and France (4.4% *vs* 6.5%, $P = 0.45$, respectively), median invasive mechanical ventilation duration and mean PICU length of stay were shorter in Canada (4 d *vs* 6 d, $P = 0.02$ and 5.7 d *vs* 8.2 d, $P = 0.03$, respectively). H1N1pdm09 vaccination prior to PICU admission was associated with a decreased risk of requiring invasive mechanical ventilation (OR = 0.30, 95%CI: 0.11-0.83, $P = 0.02$).

CONCLUSION
The critical illness due to H1N1pdm09 had a higher incidence in Canada than in France. Critically ill children were less likely to have received vaccination prior to hospitalization in comparison to general population and children vaccinated had lower risk of ventilation.

Key words: Vaccine; Children; Intensive care; Critical care; Influenza; Pandemic

Core tip: This article is on a two national cohorts study from Canada and France of critically ill children during influenza pandemic and reports that: (1) critically ill French children were much less likely to have received vaccine prior to hospitalization against influenza A(H1N1)pdm09 in comparison to children in the Canadian populations; and (2) in Canada, where vaccination rate was higher, the risk of severe respiratory failure was less among those critically ill children receiving vaccine.

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INTRODUCTION

By March 2009, pandemic influenza A(H1N1)pdm09 had begun to spread from Mexico across the globe. The epidemiology of the first pandemic wave in Canada revealed that A(H1N1)pdm09 affected both young healthy patients and patients with underlying conditions. The severity of illness among children was high, predominantly due to severe hypoxic respiratory failure, resulting in prolonged pediatric intensive care unit (PICU) length of stay and mechanical ventilation, in comparison with seasonal influenza[1]. Countries from the Southern Hemisphere also reported early patterns of severity of illness including higher mechanical ventilation rate and higher mortality than previously observed with seasonal influenza[2,3].

To limit the impact of the pandemic influenza A(H1N1)-pdm09 especially on children[4-6], a vaccination campaign was conducted just before the second wave. However, different vaccine coverage across countries was observed, especially between Canada and France[7-10]. In order to study the impact of pandemic influenza H1N1 vaccination prior to hospitalization on critical illness, we conducted a bi-national observational study in 42 centers across Canada and France on pandemic influenza A(H1N1)-associated critically illness in children, the most sensitive population affected by the pandemic. We originally hypothesized that the higher rate of vaccination coverage in children in Canada and previous exposure to influenza A(H1N1)pdm09 would have protected Canadian children from critical illness in the Fall of 2009.

MATERIALS AND METHODS

Ethical considerations

The participating institutions' research ethics boards approved study procedures in the two countries (Sainte-Justine IRB and Bordeaux IRB). The need for informed consent was waived given the non-interventional study design.

Study design

We studied pandemic influenza A(H1N1)pdm09 incidence and severity in children in Canada and France using two multicenter national databases designed for pandemic surveillance. A key difference between the two countries was that 54% of children in Canada and 18% in France had been vaccinated[7-10]. On the other hand, Canada and France are two similar industrialized countries with a gross domestic product par capital ranking, 15th and 23rd rank in the world, respectively - with similar per capita health expenditures[11,12]. Their climates during autumn are similar (average temperatures (low/high) are 0 ℃ to 15 ℃ in Canada and 5 ℃ to 20 ℃ in France). France and Canada have similar health care systems in that they are based on social health insurance to provide near universal coverage to the adult and pediatric populations. Family practitioners provide primary health care in each country and most vaccine delivery does not require out-of-pocket payment. The number of PICU is also similar (2.9 bed/100000 children under 15 years in Canada and 2.5 beds per 100000 children in France)[9,13]. During the pandemic, treatment recommendations were the

same, those of the World Health Organization. Although oseltamivir was not prescribed initially to children under two years of age in Canada, and under one year of age in France, as of October 27, 2009 in Canada and December 10, 2009 in France, these restrictions were abolished[14,15]. Vaccination campaigns were organized in the two countries with the same priority groups and guidelines[16-18]. The campaigns started on October 18, 2009 in Canada and October 20, 2009 in France[19].

Data collection was prospective in all Canadian PICUs (n = 17). In France, data collection was both prospective and retrospective in 25 of 29 French PICUs. Four French PICUs did not participate to the study. All children admitted to a participating PICU in Canada and France, with documented A(H1N1)pdm09 infection between October 1 2009 and January 31 2010, were included. During this second wave of pandemic influenza A(H1N1)pdm09, all children admitted to PICU with clinical symptoms of H1N1 infection or strong epidemiologic link to patients with known H1N1 infection were tested for H1N1, in both countries. Proven A(H1N1)pdm09 corresponded to World Health Organization criteria in both countries: Any specimen yielding influenza A(H1N1)-pdm09 by polymerase chain reaction and/or viral culture[20]. Variables in common between both databases were identified.

Data collection and outcomes

The data collected in both cohorts included demographic characteristics, vaccination history, comorbid conditions, admission severity of illness according to the Pediatric Logistic Organ Dysfunction (PELOD)[21] and Pediatric Index of Mortality 2 (PIM2)[22] scores, and intensive care management conditions. The geographic area of 17 Canadian PICUs corresponded to a pediatric population of almost 6 millions children[23] and the 25 French PICUs cover a pediatric population of almost 11 millions children[24]. We also collected data on infection severity including acute respiratory distress syndrome (ARDS) that is characterized by an acute hypoxemia due to lung inflammation[1] in reaction to viral infection or secondary bacterial infection, nosocomial infection that could result from invasive treatments and seizures.

The study's primary objective was to assess whether vaccination prior to hospitalization protects against critical illness. The secondary outcomes were A(H1N1)pdm09 incidence, the timing of the epidemic peak and the epidemic duration, PICU mortality, the incidence and duration of invasive mechanical ventilation, PICU length of stay between the two countries. Mechanical ventilation was considered invasive if delivered through an endotracheal tube or a tracheostomy. The duration of each episode of mechanical ventilation was defined as the time from intubation to final extubation or death. Mechanical ventilation was considered non-invasive if delivered through a nasal or facemask interface. Total duration of ventilation corresponded to the sum of the periods of both invasive and non-invasive ventilation.

Statistical analysis

Descriptive statistics included counts and proportions, means (and standard deviations), medians (and inter-quartile ranges) as appropriate. Incidence and incidence curves were calculated using as a denominator, the number of susceptible patients in the population in each country from Statistics Canada and the "Institut National de la Statistique et des Etudes Economiques" in France. We compared the two countries using bi-variate analysis including Pearson's χ^2 test or Fisher's exact test for categorical variables. Student's t-test, Wilcoxon rank-sum test or the log-rank test, were used for continuous variables. To assess associations between patient or country factors and outcomes, we performed a multivariate logistic regression for invasive ventilation risk and Cox proportional hazards modeling for time-dependent variables such as length of stay and invasive ventilation duration. Because data came from two different cohorts, there was heterogeneity in data distributions, requiring country-specific analyses for many variables. Variables used in final multivariate models met the following criteria: Factors of clinical interest or possibly associated with the outcomes ($P < 0.1$ in univariate analysis), more than 3 cases per group and per country, and with few (< 5%) missing values in each country. All variables were tested for excessive (> 0.80) co-linearity. For Cox regression modeling, variables respected the proportional hazards assumption. Analyses were considered statistically significant at $\alpha < 0.05$. SPPS version 19 was used for all analyses. The statistical methods of this study were performed by a biomedical statistician (Thierry Ducruet from Sainte-Justine Hospital, co-author).

RESULTS

Epidemiologic data

In total 285 children were included, 160 in Canada and 125 in France. The rate of admission to PICU due to A(H1N1)pdm09, calculated using the estimated population studied (see methods), was 2.63 per 100000 children in Canada and 1.15 per 100000 children in France (Table 1). The incidence curves showed a higher peak (41 *vs* 17 admissions per week, both during week 45) but shorter pandemic period (6 wk *vs* 11 wk) in Canada compared to France (Figure 1).

Baseline characteristics and health status on admission (Table 1)

The sex ratios and age distribution of critically ill children were similar in Canada and in France. After vaccination program start (Figure 1), vaccination coverage prior to hospitalization of children admitted to PICU was higher in Canada than in France (21% *vs* 2% of children respectively, $P < 0.001$), and in both countries, this vaccination coverage was substantially lower than that of the general pediatric population ($P < 0.001$, using conservative estimates of 54% in children in Canada and 18% in

Table 1 Characteristics of critically ill children with influenza A(H1N1)pdm09 virus at admission to the pediatric intensive care unit in two countries

	Canada (*n* = 160)	France (*n* = 125)	OR (95%CI) Canada/France	*P* value
Incidence rate (/100000 children)	2.6	1·1	2.3 (1.8-2.9)	< 0.001
Age, mean (SD), yr	6.6 (0.40)	5.5 (0.48)	NA	0.09
Weight, mean (SD), kg	25.9 (1.62)	20.1 (1.45)	NA	0.01
Female gender, *n* (%)	68 (42)	56 (45)	0.91 (0.57-1.46)	0.70
Vaccination H1N1, *n* (%)	34 (21)	2 (2)	16.6 (3.90-70.6)	< 0.001
Underlying chronic conditions, *n* (%)				
Any underlying conditions	102 (64)	93 (74)	0.60 (0.36-1.01)	0.05
Infant < 1 years old	21 (13)	32 (25)	0.44 (0.24-0.81)	0.007
Lung disease	65 (40)	29 (23)	2.26 (1.34-3.82)	0.002
Asthma	42 (26)	16 (13)	2.40 (1.29-4.56)	0.005
Chronic lung disease	33 (20.6)	14 (11.2)	2.06 (1.05-4.05)	0.03
Cystic fibrosis	0 (0)	2 (2)	NA	NA
BPD	4 (2)	4 (3)	0.78 (0.19-3.16)	0.73[1]
Tracheostomy	5 (3)	1 (1)	4.00 (0.46-33.3)	0.24[1]
Congenital heart disease	24 (15)	3 (2)	7.18 (2.11-24.4)	< 0.001
Neurological disease	31 (19)	19 (15)	1.33 (0.71-2.50)	0.36
Seizure disorder	19 (12)	5 (4)	3.23 (1.18-9.09)	0.02
Immunosuppressive disorder	11 (7)	9 (7)	0.95 (0.38-2.37)	0.91
Diabetes mellitus	6 (3.8)	0 (0)	NA	0.04[1]
Renal insufficiency	7 (4)	1 (1)	5.56 (0.69-50.0)	0.08[1]
Others diseases	32 (20)	28 (22)	0.87 (0.95-1.54)	0.62
PELOD score, mean (SD)[2]	6.67 (0.82)	7.80 (1.47)	NA	0.47
PIM2 score, mean (SD)[3]	8.47 (1.05)	9.74 (2.77)	NA	0.67
Clinical presentation at admission				
Lower respiratory infection, *n* (%)	101 (63)	90 (72)	0.67 (0.40-1.10)	0.11
CNS infection	2 (1)	7 (6)	0.21 (0.04-0.99)	0.04
Shock	13 (8)	6 (5)	1.75 (0.65-4.76)	0.26
Other	48 (30)	35 (29)	1.10 (0.67-1.85)	0.90
Bacterial infection at admission	22 (14)	27 (22)	0.58 (0.31-1.07)	0.08

[1]Fisher's exact test; [2]Missing values PELOD: 42.4% in France, 1.9% in Canada; [3]Missing values PIM2: 37.6% in France, 0% in Canada. Chronic lung disease = chronic restrictive lung syndrome and chronic upper airway disease and tracheo/bronchomalacia and obstructive sleep apnea and recurrent aspiration into lungs and others; Immune deficit = oncologic disorder and HIV and hemoglobinopathy. CI: Confidence interval; NA: Not applicable; BPD: Broncho-pulmonary dysplasia; PELOD: Pediatric logistic organ dysfunction; PIM2: Paediatric index of mortality revised version; OR: Odds ratio; SD: Standard deviation.

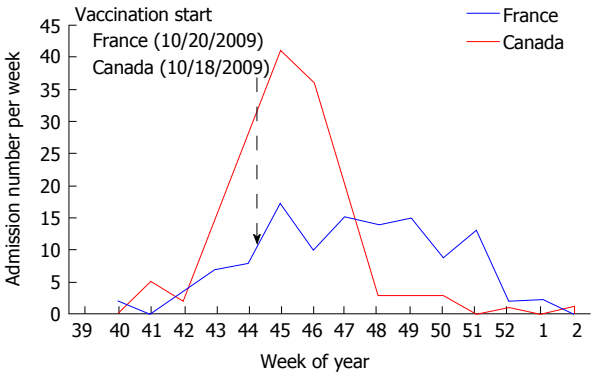

Figure 1 Admission number per week in pediatric intensive care units in Canada (red line) and France (blue line). In Canada, the decrease in incidence starts 2 wk after vaccination campaign start.

France[7-10]). Co-morbid conditions were common in both Canada and France but individual distributions were different.

Clinical presentation and hospital course

The most common reason for PICU admission was lower respiratory infection in both Canada (63%) and France (72%) and clinical presentations at admission were similar between the two countries (Table 1). The mean organ dysfunction score (PELOD score) at day one and mean predicted mortality score (PIM2 score) were similar. During hospitalization, there was a higher rate of severity of illness in France: ARDS, nosocomial infection, nosocomial pulmonary infection, and seizures (Table 2).

Outcomes

Mortality rate (4.4% *vs* 6.5%, *P* = 0.45) and rate of invasive mechanical ventilation (49% *vs* 40%, *P* = 0.14) were similar in Canada and France (Table 2). The duration of invasive mechanical ventilation (median, 4 d *vs* 6 d, *P* = 0.02) and total (invasive and non-invasive) mechanical ventilation (4 d *vs* 5 d, *P* = 0.07) was shorter in Canada than in France (Table 2). The mean PICU length of stay was shorter in Canada (5.7 d *vs* 8.2 d, *P* = 0.03) but median PICU length of stay was not different (3 d *vs* 2.9 d).

Among Canadian patients, independent multivariate analyses showed that H1N1 vaccination and asthma were associated with an almost four-fold decrease risk of invasive ventilation: (OR = 0.3, 95%CI: 0.11-0.83, *P* = 0.02) and (OR = 0.23, 95%CI: 0.09-0.64, *P* = 0.004), respectively (Table 3). This multivariate analysis did not include French patients because there were only 2

Table 2 Hospital course of critically ill children with influenza A(H1N1)pdm09 infection in two countries

	Canada (n = 160)	France (n = 125)	OR (95%CI), difference	P value
Time-dependent variables, median (25th 75th percentile), d				
PICU length of stay	2.9 (2.1-3.6)	3.0 (1.8-4.2)	0.1	0.03
Duration of mechanical ventilation	4.0 (2.8-5.2)	5.0 (3.2-6.8)	1	0.07
Duration of invasive ventilation	4.0 (2.9-5.1)	6.0 (4.6-7.4)	2	0.02
Categorical variables, n (%)				
Mortality	7 (4.4)	8 (6.5)	0.67 (0.24-1.90)	0.45
Respiratory dysfunction				
ARDS	29 (18)	40 (32)	0.48 (0.27-0.81)	0.007
Mechanical ventilation	86 (54)	66 (53)	1.04 (0.67-1.67)	0.87
Invasive ventilation	78 (49)	50 (40)	1.43 (0.91-2.50)	0.14
Pneumothorax	19 (12)	10 (8)	1.17 (0.67-3.33)	0.32
ECMO	3 (2)	8 (6)	0.28 (0.07-1.07)	0.05
Neurologic dysfunction				
Seizures	2 (1)	9 (7)	0.16 (0.03-0.13)	0.01
ADEM	3 (2)	7 (6)	0.32 (0.08-1.26)	0.09
Renal dysfunction				
Dialysis/hemofiltration	10 (6)	4 (3)	2.00 (0.63-6.67)	0.24
Nosocomial infections				
Nosocomial infection	15 (9)	26 (21)	0.39 (0.20-0.78)	0.006
Ventilator-associated pneumonia	9 (6)	21 (17)	0.29 (0.13-0.67)	0.002
Antiviral treatment				
Oseltamivir	148 (93)	111 (89)	1.55 (0.69-3.49)	0.28
Oseltamivir within 48 h	102 (63)	99 (79)	0.46 (0.27-0.79)	0.004

A bivariate analysis compared mortality, organ dysfunction, nosocomial infection and anti-viral treatment between the two countries. OR: Odds ratio; CI: Confidence interval; PICU: Pediatric intensive care unit; ARDS: Acute respiratory distress syndrome: ECMO: Extracorporeal membrane oxygenation; ADEM: Acute demyelinating encephalo-myelitis or demyelinating disorder.

Table 3 Critically ill patient-based factors associated with risk of invasive ventilation in Canada

Included variables	n = 157	OR	95%CI	P value
PIM2 > 7.5	39	6.26	2.43-16.4	< 0.001
Age, years < 1	21	1.88	0.51-6.94	0.35
1-4	52	1.50	0.51-4.35	0.46
5-9	46	2.42	0.45-6.93	0.10
> 10	38	1	(Ref)	
H1N1 vaccine	32	0.30	0.11-0.83	0.02
Asthma	41	0.23	0.09-0.64	0.004
Lung diseases (not asthma)	22	0.99	0.32-3.08	0.99
Neurologic diseases	31	2.51	0.92-6.90	0.07
Cardiologic diseases	28	1.13	0.43-2.97	0.76
Others diseases	47	0.87	0.37-2.05	0.76
Oseltamivir within 48 h	102	1.02	0.47-2.24	0.95

H1N1 vaccine, children vaccinated against H1N1; lung diseases, chronicle lung diseases without asthma; Neurologic disease, neurologic and muscular disorder; Cardiologic diseases, cardiologic diseases before admission; other diseases, all comorbities without lung, cardiologic or neurologic diseases. OR: Odd ratio; CI: Confidence interval; PIM2: Paediatric index of mortality revised version.

children in the vaccine group (Table 1).

DISCUSSION

Key findings

In this bi-national observational study of pandemic influenza A(H1N1)-associated critically illness in children, we found that pandemic influenza A(H1N1) vaccination prior to hospitalization was less common among critically ill children when compared to the general paediatric population, and that history of vaccination was not associated with a clinically relevant difference in PICU length of stay (0.1 d). However, in Canada, with higher vaccine coverage among critically ill patients, the PICU course seems less severe (shorter duration of invasive mechanical ventilation and PICU stay, lesser development of ARDS, and fewer subsequently acquired bacterial infections) (Table 2).

Despite a higher vaccine coverage and potential previous exposure to the virus in Canada during the first pandemic wave in the Spring of 2009[1], the incidence of admission of critically ill children to intensive care due to Influenza A(H1N1)pdm09 during the Fall of 2009 was twice as high in Canada as in France (2.6 per 100000 children *vs* 1.1 per 100000 children). However, the mortality rate for these critically ill children was similar between the two countries.

We originally hypothesized that the higher child vaccination coverage in Canada (> 50% *vs* 18% in France) and previous exposure to influenza A(H1N1)-pdm09 would have protected Canadian children from critical illness in the Fall of 2009. We did not observed such a protection. This hypothesis was based on the following arguments: (1) previous exposure to influenza A(H1N1)pdm09 would have increased herd immunity; (2) adjuvant pandemic vaccine has an efficacy up to 97%[25-27]; (3) an influenza vaccination coverage rate above 45% reduces influenza transmission[28]; and (4) modeling studies suggested that the vaccination campaign was associated with a decrease in mortality and morbidity of 20% and 18% respectively[29]. Other factors previously identified as contributing to outbreak

spread such as proximity to the first infectious focus, human mobility, reproduction number, generation time, population susceptibility, age pyramid, school calendar, and climate[30] were similar between the two countries and the underlying characteristics of the children were similar (Table 1). Given that the difference in incidence of PICU admission was the opposite of what was expected, our study suggests that additional national, geography-specific, and/or further unappreciated factors likely exhibit substantial residual influence on the incidence of pandemic influenza in differing regions of the world.

It has also been shown that the virulence of influenza A(H1N1)pdm09 strains virulence can vary considerably in animals and in humans[31-35]. Some specific strains were associated with severe disease in Canada and France but the proportion of these virulent strains in Canada and France is incompletely reported. Differing virulence could have contributed to the increased incidence of critical illness in Canada, as well as to the higher mortality observed in Argentina and Turkish pediatric cohorts when compared with those in North America, Europe and Australia and New Zealand[36-39].

Despite the higher incidence of critical illness in Canada when compared to France, our study provides some arguments on the positive impact of vaccine on influenza critical illness in children, even when the vaccine is given when pandemic second wave has already started (Figure 1). Our study showed that: (1) the second wave ended earlier than in France, which had a lower vaccine coverage; (2) vaccination coverage was substantially lower in the PICU population than in the general pediatric population; (3) total duration of mechanical ventilation was shorter in Canada; and (4) vaccination was associated with a decreased risk of invasive mechanical ventilation (Table 3). As expected, asthma was also associated with a decreased risk of invasive ventilation. This is consistent with previous findings of a low rate (4.6%) of invasive mechanical ventilation in PICU patients admitted for acute asthma[40]. The significant association between vaccination coverage and reduction in invasive mechanical ventilation is remarkable considering that the rate of invasive mechanical ventilation in children without a diagnosis of asthma diagnosis in this study was > 40%.

Strengths and weaknesses of the study

This study has several strengths: (1) It represents the largest pediatric cohort of critically ill H1N1 infection yet described in Canada and France; (2) the evolution of new H1N1 cases per week in PICUs (Figure 1) was similar to the consultations rates for influenza-like illness in the general population of Canada and France[41,42]; and (3) there was a large difference in vaccine coverage. This difference in coverage may be attributed to differences in perception of risk amongst the population such as awareness of the public health issues, the risk of being infected by the virus, the risk of severe illness if infected, and the risk of harm from a pandemic vaccine[43,44].

Our study has several limitations that should be noted. First, the suspected difference in virulence between the two countries could have created a bias on the analysis of pandemic vaccine impact. However, the analysis of critically ill children in Canada only provided an association between vaccine delivery and reduction in the risk of invasive ventilation (Table 3); second, admission criteria in PICUs are not standardized across countries and this can impact the incidence of PICU admission and inferred critical illness. However, several arguments suggest that admission criteria between Canada and France are similar, including: (1) the similar number of PICU beds per capita; and (2) patients displayed similar organ failure score (PELOD score) and predicted risk of mortality (PIM2) on admission to PICU (Table 1). Interestingly, this difference in ICU admission rate was also observed in adult intensive care units, with a rate of A(H1N1)pdm09-associated admission of 3.5/100000 population in Canada and 2.1/100000 population in France (OR = 1.7)[45,46]. Another limitation is that the two national cohorts used similar but not identical case report forms. Therefore, we needed to compare similar variables that may have been collected in slightly different ways in order to compare the two cohorts. In order to address this point for future outbreaks and pandemics, a number of national critical care research consortia initiated the International Forum of Acute Care Trialists which seeks to improve the care of acutely ill patients around the world by harmonizing case report forms and definitions[47]. This goal has been further advanced by the creation of International Severe Acute Respiratory and Emerging Infection Consortium.

In conclusion, the critical illness due to H1N1pdm09 had a higher incidence in Canada than in France. In both Canada and France, critically ill children were much less likely to have received vaccination against influenza A(H1N1)pdm09 prior to hospitalization when compared with children in the general population. In Canada, with higher vaccine coverage among critically ill patients, the PICU course seems less severe and the risk of invasive mechanical ventilation was lower amongst Canadian critically ill children receiving prior vaccination. There is a need for further studies to confirm our observations as numerous and still uncertain factors influence differences in pandemic influenza incidence and severity in different regions of the world, even in countries with similar population characteristics, access to health care resources and response systems.

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COMMENTS

Background

By March 2009, pandemic influenza A(H1N1)pdm09 had begun to spread from Mexico across the globe. The epidemiology of the first pandemic wave in Canada revealed that A(H1N1)pdm09 affected both young healthy patients and patients with underlying conditions. To limit the impact of the pandemic influenza A (H1N1)pdm0 especially on children, a vaccination campaign started when the second wave occurred. A lot of discussions criticized the vaccination campaign policy.

Research frontiers

Nowadays, Bird flu could combine with human flu to create a virulent kind of super-flu that can spread worldwide. The information gathered from previous pandemic (including the authors' study) are helpful to predict the spread and severity of such a risk.

Innovations and breakthroughs

This study report data on: (1) the incidence of critically ill children with pandemic influenza A (H1N1)pdm09 infection that was not known in Europe and Canada; (2) on mortality rate were higher in South American and Turkish studies; and (3) a positive impact of vaccination, even if started at second wave start, was not previously described in critically ill children.

Applications

According to the results, in case of pandemic, it is recommended to perform the flu vaccination as soon as the vaccine is available to potentially decrease disease severity.

Terminology

H1N1pdm09 infection: Flu pandemic; PICU: Pediatric intensive care units; ARDS: An acute hypoxemia due to lung inflammation.

Peer-review

The study is well designed with detailed methodology to assess the impact of vaccination status on severity of infection and mortality rates.

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