

Clinical Attack Rate and Presentation of Pandemic H1N1 Influenza versus Seasonal Influenza A and B in a Pediatric Cohort in Nicaragua

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Background. Little is known about the clinical presentation and epidemiology of influenza A H1N1pdm in children in developing countries. We assessed the severity of influenza A H1N1pdm in children in Nicaragua by comparing H1N1pdm cases to seasonal influenza cases in an ongoing cohort study.

Methods. The Nicaraguan Influenza Cohort Study was established in June 2007 to study the burden and seasonality of pediatric influenza in a tropical developing country. During the period from June 2007 through November 2009, a total of 4391 children aged 2–14 years participated in the cohort. We examined the attack rate of clinical influenza and assessed symptoms at first presentation in febrile patients with H1N1pdm versus those with seasonal influenza A or B.

Results. The estimated clinical attack rate of H1N1pdm in the cohort was 20.1%, compared to 11.7% and 15.1% for seasonal influenza A and 11.9% and 24.2% for seasonal influenza A and B in 2007 and 2008, respectively. Symptoms significantly associated with H1N1pdm cases versus seasonal influenza A cases were sore throat (adjusted odds ratio [OR], 1.7; 95% confidence interval [CI], 1.2–2.5), wheezing (OR, 5.1; 95% CI, 1.3–19.0), rhonchi (OR, 4.6; 95% CI, 1.4–15.0), crepitations (OR, 16.2; 95% CI, 2.1–128.7), pneumonia (OR, 8.0; 95% CI, 1.7–37.3), nausea (OR, 2.8; 95% CI, 1.5–5.1), and loss of appetite (OR, 2.1; 95% CI, 1.4–3.1). In addition, 3 concurrent influenza and dengue virus coinfections were identified.

Conclusions. Children with influenza A H1N1pdm presented with significantly more symptoms of lower respiratory infection and gastrointestinal symptoms than children with seasonal influenza. The clinical influenza attack rate was high in both pandemic and seasonal years.

In April of 2009, a severe outbreak of influenza, caused by a new influenza virus subtype influenza A H1N1pdm, occurred in Mexico [1]. Since that time, H1N1pdm has rapidly spread around the globe, causing the World Health Organization to declare a pandemic in June 2009 [2]. Currently, the burden that influenza A H1N1pdm will have on children throughout the world is unknown. A number of reports exist on the clinical presentation of hospitalized patients [3–7]; however, to date, little

published information exists on the clinical presentation at the community level, especially in developing countries [8], or on the attack rate of H1N1pdm [9].

Clinical attack rates of seasonal influenza in the general population typically range from 7% to 18% [10–12], whereas attack rates for pandemic influenza are estimated to range from 20% to 50% [13–15]. In both interpandemic and pandemic years, the highest attack rates have been documented in children [10, 13, 14].

Here, we describe a cohort in Nicaragua, currently in its third year, which is unique because of its large size, location in a tropical developing country, and ongoing time period spanning both seasonal and pandemic influenza epidemics. We report the clinical attack rate and presentation of febrile H1N1pdm in a cohort of children in Managua, Nicaragua, and we briefly document influenza and dengue virus coinfections that oc-

Received 13 January 2010; accepted 3 April 2010; electronically published 26 April 2010.

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Clinical Infectious Diseases 2010;50(11):1462–1467

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1058-4838/2010/5011-0006\$15.00
DOI: 10.1086/652647

curred in the cohort. To examine differences in the clinical presentation of seasonal influenza and influenza A H1N1pdm, we conducted a case-control study nested in an ongoing community-based pediatric cohort study of influenza in urban Nicaragua.

METHODS

Study population and procedures. The Nicaraguan Influenza Cohort Study (NICS) began in June 2007 to study the burden and seasonality of pediatric influenza in Nicaragua [16]. The study was established by adding influenza testing to an existing dengue cohort study, the Pediatric Dengue Cohort Study, which includes ~3800 children aged 2–14 years in Managua, Nicaragua. Children were eligible to participate in the Pediatric Dengue Cohort Study if they were within the study age range, lived in the catchment area of the Health Center Sócrates Flores Vivas, had no immunocompromising conditions (eg, current chemotherapy), and had no plans to move out of the area. Only children participating in the Pediatric Dengue Cohort Study were eligible for the NICS study. At enrollment, participants' families agreed to bring their child to study physicians at the study health center at the first sign of illness. Children are provided with medical care free of charge through the study, and data from all medical visits are collected systematically on data collection forms. At each medical appointment, data is collected on >80 symptomatic variables, including temperature, vital signs, and respiratory, gastrointestinal, and systemic symptoms.

Clinical pneumonia was diagnosed using the World Health Organization definition of a respiration rate of ≥ 40 breaths per minute with cough or difficulty breathing for children aged ≤ 5 years. For children aged ≥ 5 years, the definition consisted of ≥ 30 breaths per minute combined with abnormal auscultatory findings. The testing criteria used for influenza was fever or a history of fever with ≥ 1 of the following symptoms: cough, sore throat, or rhinorrhea. Because of resource limitations, it was not possible to test all children in the cohort study presenting with the testing criteria; therefore, 25% of the children presenting with the criteria were selected for testing through randomization. Randomization was performed with R software (R Foundation for Statistical Computing) using sampling with replacement; thus, each child meeting the testing definition had an independent 25% probability of being selected for testing. Nasal and throat swab specimens were collected from all children selected for respiratory testing. Both swabs were placed in viral transport media, stored at 4°C, and transported to the National Virology Laboratory at the Nicaraguan Ministry of Health—typically on the day of collection, but in all cases within 72 h. At the National Virology Laboratory, samples were tested by reverse-transcription polymerase chain reaction (RT-

PCR) for seasonal influenza viruses and by real-time RT-PCR for H1N1pdm viruses, in accordance with validated Centers for Disease Control and Prevention protocols [17]. Written informed consent was obtained from the parent or guardian of each participant, and verbal assent was obtained from participants aged ≥ 6 years. This study was approved by the institutional review boards at the University of California, Berkeley, and the Nicaraguan Ministry of Health.

Cases and controls for symptoms analysis. Case subjects were defined as those children in the cohort who had laboratory-confirmed cases of influenza A H1N1pdm and who met the testing definition. Control subjects were defined as those children in the cohort who had laboratory-confirmed cases of seasonal influenza A or influenza B and who met the testing definition.

Statistical analysis. The primary measures examined in this study were the clinical attack rate and the odds ratio (OR). The total number of influenza cases was determined by estimating the total number of influenza cases per week and summing across all weeks. The number of influenza cases per week was determined by applying the probability of being positive for influenza virus when tested, in which tested children constituted ~25% of the children presenting in a given week (randomization procedures are detailed in the “Study population and procedures” subsection above), to the number of children who presented meeting the testing criteria. This method assumes that being tested is independent of having positive results, conditional on the week and on meeting the testing criteria. The clinical attack rate was calculated by dividing the estimated number of influenza cases by the total number of participants. Cohort members included in the attack rate analysis were limited to those participants who were active in the cohort for the entire period of the first wave of the pandemic (June–November 2009) or the same period in 2007 and 2008. Logistic regression and multivariable logistic regression were

Table 1. Baseline Characteristics of Participants

Characteristic	Children with H1N1pdm infection (n = 185)	Children with seasonal influenza A (n = 300)	P
Sex			.45
Male	99 (54)	150 (50)	
Female	86 (46)	150 (50)	
No. of days from onset to presentation			.145
0	46 (25)	69 (23)	
1	112 (61)	159 (53)	
2	17 (9)	49 (16)	
3	8 (4)	16 (5)	
≥ 4	2 (1)	7 (2)	

Table 2. Distribution and Odds Ratios (ORs) for Symptoms of H1N1pdm Influenza versus Seasonal Influenza A

Symptoms	Children with H1N1pdm influenza (n = 185)	Seasonal influenza A (n = 300)	P	OR (95% CI)	
				Crude	Adjusted ^a
Systemic					
Arthralgia	11 (6)	27 (9)	.297	0.6 (0.3–1.3)	0.6 (0.3–1.3)
Myalgia	9 (5)	24 (8)	.199	0.6 (0.3–1.3)	0.6 (0.3–1.3)
Earache	1 (1)	8 (3)	.163	0.2 (0.0–1.6)	0.2 (0.0–1.7)
Respiratory					
Cough	173 (94)	277 (92)	.626	1.2 (0.6–2.5)	1.2 (0.6–2.6)
Sore throat	109 (59)	134 (45)	.002	1.8 (1.2–2.6)	1.7 (1.2–2.5)
Rhinorrhea	158 (85)	272 (91)	.076	0.6 (0.3–1.1)	0.6 (0.4–1.1)
Wheezing	9 (5)	3 (1)	.013	5.1 (1.4–18.9)	5.1 (1.3–19.0)
Rhonchi	10 (5)	4 (1)	.012	4.2 (1.3–13.7)	4.6 (1.4–15.0)
Crepitations	10 (5)	1 (0)	<.001	17.1 (2.2–134.6)	16.2 (2.1–128.7)
Pneumonia	10 (5)	2 (1)	.002	8.5 (1.8–39.3)	8.0 (1.7–37.3)
Gastrointestinal					
Nausea	32 (17)	20 (7)	<.001	2.9 (1.6–5.3)	2.8 (1.5–5.1)
Diarrhea	5 (3)	5 (2)	.435	1.6 (0.5–5.7)	1.5 (0.4–5.4)
Vomiting	21 (11)	42 (14)	.399	0.8 (0.5–1.4)	0.8 (0.4–1.3)
Abdominal pain	19 (10)	31 (10)	.982	1.0 (0.5–1.8)	1.0 (0.5–1.8)
Loss of appetite	98 (53)	109 (36)	<.001	2.0 (1.4–2.9)	2.1 (1.4–3.1)

NOTE. Statistically significant variables are presented in boldface font. CI, confidence interval.

^a Adjusted for the day of presentation after onset of illness.

used to determine crude and adjusted ORs. In multivariable models, the day of presentation after onset of illness was categorized as the day of illness, 1 day after onset, or ≥ 2 days after onset. Because of the longitudinal nature of the study, some children presented with influenza more than once. To assess the effect of participants presenting with influenza multiple times, several subanalyses were performed in addition to the main analysis that treated each observation as an unrelated case. First, an analysis limited to the first influenza episode was performed and second, generalized estimating equations with a binomial distribution were used to adjust for the correlation between observations. Because no significant difference was seen between the main analysis and the subanalyses, all reported estimates are from the main analysis. Comparisons between groups used the χ^2 or Fisher exact test, as appropriate. A non-parametric test for trend was used to examine the age distribution of cases of H1N1pdm and seasonal influenza cases. Thirteen- and 14-year-old children were excluded from the age comparison because of differences in the cohort age structure between years. Statistical analyses were performed using Stata software, version 10.1 (StataCorp).

RESULTS

During the period from 1 June 2007 through 15 November 2009, of the 4397 children invited to participate in the NICS,

4362 children (99.2%) participated. The age distribution was similar in all years, except that there were more 13- and 14-year-old children in years 2 and 3. Among participants, 631 laboratory-confirmed influenza cases were detected that met the testing definition. Of those, 300 were seasonal influenza A cases, 146 were influenza B cases, and 185 were influenza A H1N1pdm cases (Tables 1 and 2 and Table 3, which appears only in the electronic version of the journal). The first case of H1N1pdm in Nicaragua was detected in the cohort on 1 June 2009. Additionally, there were 3 H1N1pdm cases that involved coinfection with influenza and dengue viruses. Patients with coinfections were excluded from the main symptoms analysis, although inclusion of patients with coinfection did not significantly change the results other than hospitalization rate.

The estimated clinical attack rate of H1N1pdm in the 3680 children who were enrolled in the cohort study for the entire period from 1 June 2009 through 15 November 2009 was 20.1%. In 2007 and 2008, the estimated clinical attack rate for

Table 3. Distribution and Odds Ratios (ORs) for Symptoms of H1N1pdm Influenza versus Seasonal Influenza A and B

The table is available in its entirety in the online edition of the *Journal of Infectious Diseases*.

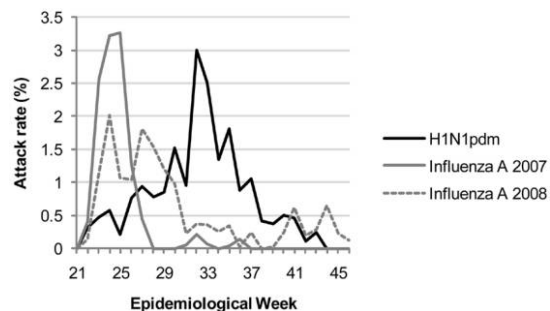


Figure 1. Weekly estimated attack rate of the first wave of influenza A H1N1pdm in the Nicaraguan Influenza Cohort Study.

influenza A was 11.7% and 15.1%, respectively; for seasonal influenza A or B, it was 11.9% and 24.2%, respectively. The weekly H1N1pdm and seasonal influenza A activity in the cohort is shown in Figure 1. Although influenza A H1N1pdm was detected in the cohort and surrounding area on 1 June 2009, peak influenza attack rates were not observed until August 2009.

The age distribution of febrile H1N1pdm cases was significantly different ($P < .001$) from the age distribution of febrile children with seasonal influenza A, with more H1N1pdm cases occurring among older children (Figure 2). There were no observed significant differences in the sex distribution or day of presentation after onset of illness between the case and control subjects (Table 1). Two (1.1%) of the children with H1N1pdm influenza and 2 (0.4%) of the children with seasonal influenza were hospitalized for pneumonia ≤ 1 week after the onset of symptoms ($P = .585$).

We examined the percentage of febrile children with H1N1pdm and seasonal influenza cases who presented with a range of systemic, gastrointestinal and respiratory symptoms. Significant differences ($P < .05$) in the percentage of children presenting with sore throat, runny nose, wheezing, rhonchi, crepitations, pneumonia, nausea, and loss of appetite were observed in children with H1N1pdm infection, compared with those who had seasonal influenza virus A infection (Tables 2 and 3). The adjusted OR was 1.7 for sore throat (95% confidence interval [CI], 1.2–2.5), 5.1 for wheezing (95% CI, 1.3–19.0), 4.6 for rhonchi (95% CI, 1.4–15.0), 16.2 for crepitations (95% CI, 2.1–128.7), and 8.0 for pneumonia (95% CI, 1.7–37.3) for children with H1N1pdm infections, compared with children who had seasonal influenza A infection, when adjusted for day after onset of symptoms. Among gastrointestinal symptoms, the OR was 2.8 for nausea (95% CI, 1.5–5.1) and 2.1 for loss of appetite (95% CI, 1.4–3.1), compared with seasonal influenza A infection, when adjusted for day after onset of symptoms.

Three influenza and dengue virus coinfections were identified during the period from 27 August 2009 through 6 October 2009. Of the 3 children with coinfections, 100% were hospi-

talized, compared with 1.1% of those with H1N1pdm infection ($P < .001$) and 42.1% of those with laboratory-confirmed dengue ($P = .080$). The age of children presenting with coinfection ranged from 3 to 13 years. All children with coinfections recovered fully.

DISCUSSION

This study describes the first wave of influenza A H1N1pdm in the NICS, examines the symptoms at presentation for febrile children with influenza A H1N1pdm versus febrile children with seasonal influenza, and derives the estimated respective clinical attack rates. The estimated clinical attack rate in the first wave of the influenza pandemic (5.5 months) was 20.1%, consistent with the high rate expected from a pandemic strain. The age distribution of cases differed between seasonal and pandemic influenza, with a higher proportion of older children presenting with H1N1pdm influenza. Overall, children with H1N1pdm influenza had a higher odds of presenting with sore throat, lower respiratory tract symptoms (eg, wheezing, rhonchi, crepitations, and pneumonia), and gastrointestinal symptoms (eg, nausea and loss of appetite).

The pandemic clinical attack rate was higher than the influenza clinical attack rate in 2007 (11.9%), a year dominated primarily by influenza A, but lower than the clinical attack rate in 2008 (24.2%), when peaks of both influenza A and influenza B occurred. When the attack rates for only influenza A are compared, the clinical attack rate in 2009 is higher than that in 2007 and 2008. It should be noted that, in 2009 during the pandemic wave, the government of Nicaragua put into effect numerous control measures, including use of oseltamivir, school closures, separate health care clinics for patients with respiratory symptoms, and contact tracing, which may have affected the transmission of influenza.

Three influenza and dengue virus coinfections were identified in the cohort study. Coinfections had not previously been identified in the cohort, most likely due to separate peak trans-

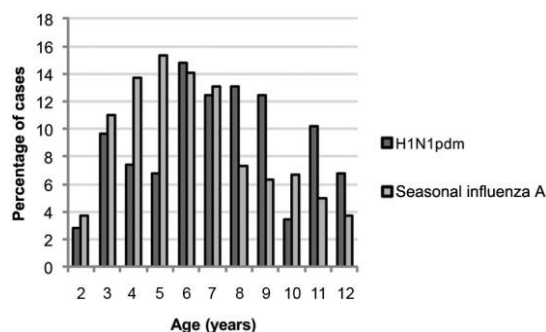


Figure 2. Percentage of laboratory-confirmed influenza A H1N1pdm and seasonal influenza A cases in each 1-year age group. Ten cases among 13- and 14-year-old children were excluded from the figure because of differences in the age structure of the cohort between study years.

mission seasons for the 2 diseases. Typically, peak influenza activity occurs from May through July [18], whereas peak dengue activity occurs from September through December [19]. However, this year—likely because of the pandemic—the peak influenza season was delayed and a substantial overlap with the peak dengue season occurred.

A major strength of our study is that the cohort study has been ongoing for several years, allowing comparison of seasonal influenza data with the introduction of H1N1pdm, because the study protocols did not change between the years of seasonal and pandemic influenza circulation. The large size of the cohort together with the use of current gold standard methods for influenza testing are additional strengths.

One limitation of this study was that the analyses depended upon the child presenting at the health center and meeting the testing criteria used in the study. Therefore, the clinical attack rate of 20% reported is undoubtedly an underestimation of the attack rate in the cohort, which includes asymptomatic or subclinical infections in addition to febrile infections. It is not possible to estimate the percentage of influenza virus infections that cause asymptomatic or subclinical infection in children, because no pediatric volunteer challenge studies of influenza have been performed. In influenza challenge studies among adults, >40% of infections are asymptomatic; however, evidence suggests that the clinical presentation of influenza in children differs significantly from that in adults [20]. Because the dengue cohort study that forms the basis of the NICS incorporates an annual blood sample from healthy children for dengue serological testing, with additional funding, we hope to be able to determine the true incidence of H1N1pdm infection by comparing the hemagglutination inhibition titers to H1N1pdm antigen in the 2009 and 2010 annual blood samples from study children. For the analysis comparing H1N1pdm cases to seasonal influenza cases, the same limitations apply regarding the need for presentation to the health center and meeting the testing criteria. However, the effect of these limitations is mitigated by the fact that the study protocols and testing criteria did not change between seasonal and pandemic years. Nonetheless, it is possible that the care-seeking behavior of parents changed during the influenza pandemic, resulting in parents being more (or less) likely to bring children in to the health center with milder symptoms than during a seasonal influenza year; this could result in a systematic bias in the study. To try to minimize this bias, we encouraged parents to always bring their children to the health center at the first sign of illness. In yearly participation surveys, only 0.8%–6.1% (mean, 2.8%) of parents reported that their child had had a fever and was not brought in for medical care [16]. Another limitation of this study is that we did not differentiate between seasonal influenza A (H3N2) and seasonal influenza A (H1N1) influenza virus, because subtyping

was not routinely performed on all samples in the study in 2007 and 2008 because of resource constraints.

In conclusion, we present the first report (to our knowledge) of the clinical attack rate and symptoms of febrile influenza A H1N1pdm in a community-based pediatric population. Taking advantage of our established pediatric cohort, we found that cohort children who had H1N1pdm influenza had a higher odds of sore throat, lower respiratory tract symptoms, and gastrointestinal symptoms, compared with cohort children who had seasonal influenza. The clinical attack rate estimated for laboratory-confirmed influenza was 20.1% for the first pandemic wave and is within the expected range. This ongoing cohort study will continue to provide essential data on influenza in the tropics.

Acknowledgments

We are grateful to Oscar Ortega, Katherine Standish, Douglas Elizondo, William Avilés, Andrea Nuñez, Mirtha Monterrey, and Josefina Coloma for their invaluable contributions to this study. We would like to thank Drs. Sergio Benito Ojeda Munguía, Luis Nery Sanchez Palma, Grethel María Navas Pasquier, and Jackeline Herrera Morales for providing medical attention to participants; and María Celina Perez Zúñigas, Carolina Flores Hernandez, Heyri Roa Solís, Moises Navarro Martinez, and Patricia Castillo Palma for laboratory assistance. In addition, we would like to thank Rain Mocello for editorial assistance, Cecile Viboud and Art Reingold for support and advice, and the study participants and their families.

Financial support. The Fogarty International Center of the National Institutes of Health, the Pediatric Dengue Vaccine Initiative, the US National Institute of Allergy and Infectious Diseases, and the Centers for Disease Control and Prevention. The sponsors of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Potential conflicts of interest. All authors: no conflicts.

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