Association of Age and Comorbidity on 2009 Influenza A Pandemic H1N1-Related Intensive Care Unit Stay in Massachusetts

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Objectives. We compared comorbidity measures by age group and risk factors for influenza-like illness (ILI)–related intensive care unit (ICU) stay during the 2009 seasonal influenza and influenza A (pH1N1) pandemic.

Methods. We identified all patients discharged from Massachusetts hospitals with ILI-related diagnoses between October 1, 2008, and April 25, 2009, and pH1N1–related diagnoses between April 26 and September 30, 2009. We calculated the Diagnostic Cost Group (DxCG) risk score as a measure of comorbidity. We used logistic regression predictive models to compare ICU stay predictors.

Results. Mean DxCG scores were similar for pH1N1 and seasonal influenza time periods (0.69 and 0.70). Compared with those aged 45 to 64 years, patients younger than 5, 5 to 12, and 13 to 18 years had an increased risk of pH1N1-related ICU stay. Within the pH1N1 cohort, an asthma diagnosis was highly predictive of ICU admission among those younger than 5, 5 to 12, and 13 to 18 years, and pregnancy among those aged 26 to 44 years.

Conclusion. High-risk groups, including children with asthma or pregnant women, would benefit from improved surveillance and resource allocation during influenza outbreaks to prevent serious ILI-related complications. (*Am J Public Health.* 2014;104:e118–e125. doi:10.2105/AJPH.2014.302197)

The emergence and spread of the novel influenza A (pH1N1) virus resulted in extraordinary influenza activity across the United States in 2009.[1] Severe influenza infection typically occurs in the very young, the elderly, and those with comorbid diseases.[2] However, studies have shown epidemiological differences between seasonal and pH1N1 patients stratified by age. The median age of hospitalized pH1N1 cases was younger than that normally seen with seasonal influenza, with infants with pH1N1 having the highest hospitalization rates.[3] In North America, 60% of all identified cases were younger than 18 years.[4] In one study, hospitalized patients with confirmed or probable pH1N1 infection ranged in age from 21 days to 86 years, but 45% of hospitalized cases were younger than 18 years, and only 5% of cases were aged 65 years or older.[5] Our previously published analysis of statewide 2009 pH1N1 epidemiological data in Massachusetts suggested that there were disproportionately large numbers of hospitalized pH1N1 cases among younger age groups.[6] Other work has shown that the pH1N1 attack rates were low in the general population, and high in children aged 5 to 19 years, and that estimated hospitalization and mortality rates per infection increased significantly with age.[7]

The 2009 pH1N1 virus is a unique virus, but studies have found similarities between this pathogen and other influenza A viruses that have circulated in the past. Serum specimens analyzed by hemagglutination-inhibition testing for the presence of antibodies against pH1N1 found that most individuals born after 1944 lacked antibodies to the pandemic virus.[8,9] These findings suggest that previous exposure to seasonal influenza viruses or previous influenza vaccination had conferred some level of protective immunity against pH1N1. Other evidence indicates that the pH1N1 virus may have originated from the Spanish influenza virus and its descendants, which could explain the partial immunity exhibited in the older population.[9]

Epidemiological assessments have shown that certain age-related trends occurred during the 2009 pH1N1 pandemic. Adults with pH1N1-related hospitalizations had significant complications and mortality despite being younger than patients with seasonal influenza.[10] However, statewide population-based comparisons of predictors of severe seasonal influenza and pH1N1 by age strata have not been conducted in the United States, and we do not yet know how comorbidity measures compare between age strata or between influenza seasons. To establish a baseline measure of comorbidity, we used validated risk adjustment calculation software, Diagnostic Cost Group (DxCG) Risk Analysis, to calculate individual-level baseline measures of comorbidity based on hierarchical condition categories (HCCs).[11]

We calculated a risk-adjusted score for each patient discharged from any Massachusetts acute care hospital with influenza-like illness (ILI) between October 1, 2008, and September 30, 2009, and compared predictors of ILI-related intensive care unit (ICU) stay by age strata. Specific study objectives included (1) compare comorbidity measures by age group for those hospitalized during the pH1N1 pandemic and seasonal influenza time period in 2009, and (2) compare risk factors for ILI-related ICU stay for those hospitalized during the pH1N1 pandemic and seasonal influenza time period.

METHODS

We analyzed data from the Hospital Inpatient Discharge Database (HIDD), which is a population-based, patient-linked listing of all hospital discharges in Massachusetts and includes up to 15 *International Classification of*

Diseases, 9th Revision (*ICD-9*)–coded discharge diagnoses for each patient.[12,13] The HIDD contains discharge data for all inpatients discharged from all 76 acute care hospitals in Massachusetts. This data source contains comprehensive information including sociodemographic data, clinical data, and charge data, with a total of 377 variables. Patients met the following inclusion criteria: (1) discharge from any acute care hospital in Massachusetts between October 1, 2008, and September 30, 2009; (2) assigned 1 or more diagnosis codes corresponding to a grouping of *ICD-9* codes used to identify ILI[12]; and (3) younger than 65 years. Nationwide US influenza data indicated that only 7% of pH1N1-related hospitalizations occurred in those aged 65 years or older,[14] so we excluded individuals in that age group from the study population to minimize misclassification bias introduced by noninfluenza cases. The following groups were categorized in the HIDD as an indicator of race/ethnicity: Non-Hispanic White Hispanic; Non-Hispanic Black; other, which includes Asian (n = 276); American Indian/Alaska Native (n = 14); other, which includes any other racial/ethnic groups not listed (n = 221); and unknown (n = 200).

Selection criteria corresponded to a variation of a list of codes validated against virologic results in a study evaluating code-based syndromic surveillance for ILI.[15] Our previous work describes the methodological process for ILI code selection.[6] The outcome was ICU admission determined by ICU-related diagnosis codes.

Age group categories were consistent with age-specific influenza reporting in Massachusetts, based on Centers for Disease Control and Prevention–defined priority groups[16] (< 5 years, 5–12 years, 13–18 years, 19–25 years, 26–44 years, 45–64 years).

Confirmed-case laboratory specimen data from the Massachusetts State Laboratory indicated that between April 19 and October 1, 2009, 34% of all submitted specimens were positive for influenza A and 99% of influenza virus isolates were pH1N1.[16] This time interval occurred before pH1N1 vaccine was released and, therefore, it represents a unique time to study the impact of the virus before the availability of immunization. Before April 26, 2009, seasonal influenza activity was common in Massachusetts: April 26 marks the first date that pH1N1 was detected, and September 30 is designated as the beginning of the influenza season for surveillance purposes.

Originally used to predict health care–related costs, the DxCG risk analysis software is an established risk adjustment model designed to calculate individual-level baseline measures of risk for hospitalization, hospital readmission, and future health care costs likely to be incurred. The DxCG model is a feasible way to calculate baseline measures of comorbidity on the basis of readily available, already audited inpatient diagnostic data, and an effective way to compare risk at baseline by age strata to control for number of high-risk conditions.

Our analysis was based on the Centers for Medicare and Medicaid Services HCC model that was implemented in 2004. The DxCG–HCC model uses data from diagnoses generated during patient hospital discharge diagnosis coding to calculate which medical problems are present in an individual and generate a risk-adjusted score based on *ICD-9* codes.[12] This score is based on values assigned to diagnostic categories that have been designed to meet several principles meeting hierarchical conditions and clinical significance. The HCC diagnostic classification system first classifies each of more than 15 000 *ICD-9* codes into 804 diagnostic groups, and these groups are further aggregated into 189 condition categories. The process of condition category selection and performance of DxCG–HCC models have been described previously.[11] The final, 70-category DxCG–HCC model, along with patient demographics such as age and gender, are used to predict measures of comorbidity or disability. In previous work, DxCG has been shown to be a more effective predictor of morbidity than other measures, such as the Charlson.[17]

As explained previously, the original DxCG–HCC model excluded discretionary diagnostic categories from its total of 189 condition categories for various methodological reasons. Some were excluded because they were not medically significant or they did not empirically add to predicted costs.[11] For the purposes of this analysis, DxCG risk scores may not capture the full picture of the burden of comorbidity that could affect the severity of influenza. Therefore, to investigate the addition of some known additional risk factors into our model, we identified risk factors for pH1N1 that were not included in the DxCG calculation. Several risk factors for severe pH1N1 have been identified including pregnancy, obesity, and asthma.[10,18] These risk factors and *ICD-9* codes were as follows: asthma (493.0), obesity (278.0), and pregnancy (630.0–679.0). We explored the prevalence of these risk factors in both the pH1N1 and seasonal influenza study populations and included dichotomous variables for these characteristics in our final model.

We identified those discharged with ILI-related diagnoses between October 1, 2008, and April 25, 2009, and pH1N1-related diagnoses between the time period of April 26 and September 30, 2009; calculated ICU admission rates; and described demographics by age group.

Our analysis plan involved 3 steps. In step 1, we utilized DxCG software to create diagnoses files with unique identifiers for each individual within the study population. After we calculated each individual score, we linked each individual's DxCG score with patient demographic data, diagnoses, and other hospital data in the HIDD by using medical record number. We then compared patient characteristics of 2 groups: those discharged between October 1, 2008, and April 25, 2009 (seasonal influenza group), and those discharged between April 26 and September 30, 2009 (pH1N1 group). In step 2, we utilized 3 models within the seasonal influenza population and pH1N1 population to identify the association between DxCG score and ICU stay and predictors of ICU stay among age groups.

Model A refers to the null model investigating the association between ICU stay and age group. Model B adds the measure of DxCG score to adjust for comorbidity measure. Model C refers to the full multivariate model investigating the association between ICU stay and age adjusted for DxCG, age, gender, specific risk factors, and source of admission into the hospital. In step 3, we applied model C to each study population and also stratified by age group to investigate age-specific predictors of ILI-related ICU stay and also to address selection bias and confounding that could occur within age-group strata. We then compared predictors of ICU stay within pH1N1 and seasonal influenza populations.

TABLE 1—Study Population Characteristics of pH1N1-Related and Hospital Discharges in Massachusetts: Hospital Inpatient Discharge Database, 2008–2009

Variable	pH1N1, No. (%) or Mean ±SD						Seasonal Influenza, No. (%) or Mean ±SD					
	All Age Groups (n = 4873)	< 5 y (n = 1178)	5–12 y (n = 355)	13–18 y (n = 214)	19–25 y (n = 345)	26–44 y (n = 953)	45–64 y (n = 1738)	All Age Groups (n = 7402)	< 5 y (n = 2060)	5–12 y (n = 456)	13–18 y (n = 287)	19–25 y (n = 389)	26–44 y (n = 1413)	45–64 y (n = 2797)
Gender														
Male	2421 (51)	699 (59)	198 (56)	94 (44)	148 (43)	439 (46)	843 (48)	3650 (49)	1190 (58)	246 (54)	124 (43)	165 (42)	599 (42)	1326 (47)
Female	2362 (49)	479 (41)	157 (44)	120 (56)	197 (57)	514 (54)	895 (52)	3752 (51)	870 (42)	210 (46)	163 (57)	224 (58)	814 (58)	1271 (53)
Race/ethnicity														
Non-Hispanic White	3070 (64)	574 (49)	180 (51)	117 (55)	117 (55)	633 (66)	1360 (78)	4909 (66)	1042 (50)	262 (57)	185 (64)	257 (66)	978 (69)	2185 (78)
Hispanic	696 (15)	267 (23)	70 (20)	34 (16)	34 (16)	130 (14)	133 (8)	1068 (15)	485 (24)	84 (18)	48 (17)	53 (14)	172 (12)	226 (8)
Non-Hispanic Black	575 (12)	150 (13)	60 (17)	39 (18)	39 (18)	120 (13)	152 (9)	816 (11)	221 (11)	62 (14)	35 (12)	49 (13)	175 (12)	274 (10)
Other	442 (9)	187 (15)	45 (12)	24 (11)	24 (11)	70 (7)	93 (5)	609 (8)	312 (15)	48 (11)	19 (7)	30 (7)	88 (6)	112 (4)
DxCG score	0.69 ±0.80	0.25 ±0.48	0.42 ±0.66	0.53 ±0.79	0.60 ±0.73	0.71 ±0.79	1.07 ±0.84	0.70 ±0.79	0.22 ±0.44	0.47 ±0.74	0.50 ±0.74	0.58 ±0.69	0.69 ±0.68	1.12 ±0.85
Deaths	28 (1)	2 (0)	2 (1)	2 (1)	2 (1)	8 (1)	12 (1)	20 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	18 (1)
ICU admissions	527 (11)	97 (8)	47 (13)	35 (16)	40 (12)	87 (9)	221 (12)	727 (10)	143 (7)	50 (11)	32 (11)	42 (11)	119 (8)	341 (12)
Source of admission														
ED transfer	2164 (45)	384 (33)	106 (30)	59 (28)	152 (44)	495 (52)	965 (53)	3025 (41)	614 (30)	124 (27)	87 (30)	164 (42)	642 (45)	1394 (50)
Direct MD transfer	1169 (24)	437 (37)	147 (41)	95 (44)	71 (21)	152 (16)	269 (15)	2021 (27)	871 (42)	206 (45)	109 (38)	88 (23)	310 (22)	436 (16)
Walk-in	797 (16)	152 (13)	46 (13)	20 (9)	69 (20)	177 (19)	334 (18)	1229 (17)	291 (14)	56 (12)	38 (13)	68 (18)	258 (18)	517 (19)
Other	743 (15)	205 (17)	56 (16)	40 (19)	53 (15)	129 (14)	170 (10)	1127 (15)	284 (14)	70 (15)	53 (19)	69 (18)	203 (14)	450 (16)
Length of stay, days	3.5 ±4.1	2.5 ±3.1	3.2 ±5.7	4.1 ±6.0	3.2 ±2.8	3.8 ±4.0	4.0 ±4.1	3.6 ±4.1	2.5 ±3.0	3.0 ±4.5	3.4 ±3.9	4.2 ±6.4	3.9 ±4.0	4.2 ±4.2

Note. DxCG = Diagnostic Cost Group; ED = emergency department; ICU = intensive care unit; MD = physician; pH1N1 = Influenza A. Influenza A–related discharges were during the period from April 26 to September 30, 2009. Seasonal influenza–related discharges were during the period October 1, 2008, to April 25, 2009.

We used a logistic regression model to provide odds estimates. Because the data source is a population-based hospital discharge data set and all discharges from all Massachusetts acute care hospitals are included in the model, we conducted a sensitivity analysis among all Massachusetts facilities to explore the level of correlation within a facility. A similar sensitivity analysis is described in our previously published work.[19]

RESULTS

Within the pH1N1-specific time period (between April 26 and September 30, 2009), 4873 individuals met inclusion criteria (Table 1). There were larger proportions of Hispanics and Blacks in those younger than 5 years than among those aged 45 to 64 years (23% and 13% vs 8% and 9%, respectively). The mean DxCG score for the study population was 0.69, and scores ranged from 0.07 to 5.80. The lowest mean score occurred in the youngest age group (0.25), and the highest mean score occurred among the oldest age group (1.07). Mean length of stay was highest among the group aged 45 to 64 years (4.0 days).

For the seasonal influenza time period, 7402 individuals met inclusion criteria between October 1, 2008, and April 25, 2009 (Table 1). Mean DxCG score was 0.70, and scores ranged from 0.07 to 5.63. Compared with the previous seasonal influenza period in Massachusetts, there were higher ICU admission rates among those younger than 18 years during the pH1N1 time period, and a higher number of deaths among those younger than 18 years during the pH1N1 pandemic (Tables 1 and 2). The DxCG scores were slightly higher among those with pH1N1 who were younger than 5 years and 13 to 18 years than among those with seasonal influenza for the same age groups (0.25 and 0.53 vs 0.22 and 0.50, respectively). Adults with pH1N1 in the groups aged 19 to 44 years and 45 to 64 years also had slightly higher DxCG scores than those with seasonal influenza for the same age groups (Table 1).

Consistent with other epidemiological reports, we found that the median age of those with pH1N1-related ICU admissions was younger than during seasonal influenza (37 vs 43 years; Table 2). Although sample sizes were

TABLE 2—Characteristics of Those With Influenza-Like Illness–Related Intensive Care Unit Admission During the pH1N1 Outbreak and Seasonal Influenza Outbreak: Hospital Inpatient Discharge Database, Massachusetts, 2008–2009

	pH1N1 (n = 527)		Seasonal Influenza (n = 727)	
Variable	No. (%) or Mean ±SD	Range	No. (%) or Mean ±SD	Range
Gender				
Male	296 (56)		403 (56)	
Female	231 (44)		322 (44)	
Race/ethnicity				
Non-Hispanic White	345 (66)		504 (70)	
Hispanic	54 (10)		82 (11)	
Non-Hispanic Black	69 (13)		70 (10)	
Other	59 (11)		69 (9)	
Age, y (median)	37		43	
< 5	97 (19)		141 (20)	
5–12	47 (9)		50 (7)	
13–18	35 (7)		32 (4)	
19–25	40 (8)		42 (6)	
26–44	87 (16)		119 (16)	
45–64	221 (42)		341 (47)	
DxCG score	1.2 ±1.2	0.07–5.80	1.2 ±1.1	0.07–5.63
Deaths	19 (4)		12 (2)	
Risk factors				
Asthma	148 (28)		174 (24)	
Obese	40 (8)		45 (6)	
Pregnant	10 (2)		6 (1)	
Length of stay, d	6.8 ±8.5	1–67	6.3 ±7.1	1–55

Note. DxCG = Diagnostic Cost Group; pH1N1 = Influenza A. Influenza A–related discharges were during the period from April 26 to September 30, 2009. Seasonal influenza–related discharges were during the period October 1, 2008, to April 25, 2009.

small, the death rate among those with pH1N1-related ICU admissions was twice that of those with ILI-related ICU admissions (4% vs 2%). Average length of stay was greater during the pH1N1 time period (6.8 days vs 6.3 days). Of the risk factors chosen, asthma was the most prevalent, occurring in 28% (n = 148) of the pH1N1 population, and 24% (n = 174) of those admitted to the ICU with seasonal influenza (Table 2). Compared with seasonal influenza, rates of pregnancy were double in the pH1N1 cohort (2% vs 1%), and overall rates of obesity were higher as well (8% vs 6%).

In the univariate model examining the association between pH1N1-related ICU stay and age group (Table 3), there was a significantly lower risk of ICU stay among patients aged 26 to 44 years and younger than 5 years compared with those aged 45 to 64 years (odds ratios [ORs] = 0.65 and 0.73, respectively). After we adjusted for comorbidity score, individuals younger than 5 years, 5 to 12 years, and 13 to 18 years were significantly more likely to have a pH1N1-related ICU stay than those aged 45 to 64 years (ORs = 1.39, 2.01, and 2.26, respectively). Females and Hispanics were at less risk for ICU stay (ORs = 0.76 and 0.66, respectively). Within the pH1N1 cohort, asthma was highly predictive of ICU admission among those younger than 5 years, 5 to 12 years, and 13 to 18 years (ORs = 2.71, 3.44, and 3.74, respectively). Pregnancy was also strongly associated with ICU admission among those aged 26 to 44 years (OR = 4.04; $P < .001$).

In the univariate model investigating the association between seasonal influenza–related ICU stay by age strata (Table 4), those younger than 5 years and 24 to 44 years were at lower risk for ILI-related ICU stay than those aged 45 to 64 years (ORs = 0.53 and 0.66, respectively). Similar to pH1N1, after we adjusted for DxCG score, risk for ILI-related ICU stay was significantly greater for individuals aged 5 to 12 years (OR = 1.49). Stratified by age group, asthma is a significant predictor of ILI-related ICU stay among those younger than 5 years (OR = 1.55). Obesity was shown to be protective against influenza-associated ICU stay among those aged 45 to 64 years (OR = 0.63).

In both cohorts, we found higher proportions of males among the groups younger than 5 years and 5 to 12 years (54% to 59%). After age 12 years, this trend reversed, and more than half of all patients discharged with ILI in both cohorts were female. In the full model investigating the association between ICU stay and independent variables, being female was protective against ILI-related ICU admission in both pH1N1 and seasonal influenza cohorts (ORs = 0.76 and 0.77, respectively), indicating that males were at increased risk for ILI-related ICU stay within the entire study population.

DISCUSSION

Our results are consistent with published reports indicating that specific trends exist with regard to influenza-associated outcomes by age, gender, and underlying health conditions.[20] To our knowledge, this is the first study to report population-based statewide outcomes by age strata in all acute care hospitals during the first wave of the pH1N1 pandemic. For all age groups and both influenza cohorts, increasing DxCG score predicted ICU admission. Therefore, as the measure of comorbidity increases, risk of ILI-related ICU stay also increases.

We found that those admitted to the ICU during the pH1N1 time period were younger than those with ILI-related ICU admission during the regular influenza season and had higher prevalence of risk factors shown to complicate or exacerbate pH1N1. There were more deaths among younger age groups during pH1N1. Although numbers are small, these figures indicate that pH1N1 attacked younger

TABLE 3—Measures of Association Between pH1N1–Related Intensive Care Unit Stay and Independent Variables, by Age Among All Discharged Patients Meeting Selection Criteria: Hospital Inpatient Discharge Database, Massachusetts, April 26–September 30, 2009

Variables	All[a] (n = 4873), OR (95% CI)			< 5 Years (n = 1178), OR (95% CI)	5–12 Years (n = 355), OR (95% CI)	13–18 Years (n = 214), OR (95% CI)	19–25 Years (n = 345), OR (95% CI)	26–44 Years (n = 953), OR (95% CI)	45–64 Years (n = 1738), OR (95% CI)
	Model A	Model B	Model C						
Age, y									
< 5	0.65* (0.50, 0.84)	1.30 (0.99, 1.7)	1.39* (1.1, 1.9)						
5–12	1.11 (0.79, 1.6)	1.90* (1.3, 2.7)	2.01* (1.4, 2.9)						
13–18	1.42 (0.97, 2.1)	2.21* (1.5, 3.3)	2.26* (1.5, 3.5)						
19–25	0.95 (0.67, 1.4)	1.40 (0.96, 2.0)	1.38 (0.94, 2.1)						
26–44	0.73* (0.56, 0.95)	0.95 (0.72, 1.2)	0.93 (0.70, 1.2)						
45-64 (Ref)	1.00	1.00	1.00						
DxCG score		2.09* (1.9, 2.3)	2.20* (2.0, 2.4)	3.73* (2.6, 5.3)	4.25* (2.6, 7.1)	2.66* (1.7, 4.2)	2.32* (1.6, 3.4)	2.24* (1.8, 2.8)	1.80* (1.6, 2.1)
Gender									
Female			0.76* (0.63, 0.93)	0.94 (0.59, 1.5)	0.57 (0.27, 1.2)	0.99 (0.42, 2.3)	1.05 (0.50, 2.2)	0.73 (0.45, 1.2)	0.73* (0.54, 0.98)
Male (Ref)			1.00	1.00	1.00	1.00	1.00	1.00	1.00
Race/ethnicity									
Hispanic			0.66* (0.47, 0.90)	0.84 (0.46, 1.6)	0.64 (0.23, 1.8)	1.30 (0.42, 4.0)	0.39 (0.11, 1.4)	0.33* (0.12, 0.88)	0.65 (0.34, 1.2)
Non-Hispanic Black			1.11 (0.82, 1.5)	1.08 (0.54, 2.1)	2.64* (1.1, 6.3)	0.60 (0.19, 1.9)	0.93 (0.36, 2.4)	1.04 (0.52, 2.1)	1.02 (0.61, 1.7)
Other			1.41* (1.1, 1.9)	1.33 (0.72, 2.5)	2.70 (0.96, 7.6)	1.42 (0.41, 4.9)	1.12 (0.28, 4.4)	1.06 (0.46, 2.5)	1.60 (0.89, 2.9)
Non-Hispanic White (Ref)			1.00	1.00	1.00	1.00	1.00	1.00	1.00
Risk factors									
Asthma			1.56* (1.3, 1.9)	2.67* (1.6, 4.3)	3.44* (1.5, 7.7)	3.74* (1.5, 9.0)	0.97 (0.40, 2.3)	1.22 (0.69, 2.1)	1.06 (0.71, 1.6)
Obese			0.93 (0.64, 1.3)	[b]	3.99 (0.32, 49.1)	1.00 (0.16, 6.1)	1.52 (0.37, 6.3)	0.92 (0.45, 1.9)	0.78 (0.47, 1.3)
Pregnant			1.92 (0.95, 3.9)	[b]	[b]	0.59 (0.1, 5.7)	1.05 (0.27, 4.1)	4.08* (1.5, 11.4)	[b]
Source of admission									
ED transfer			0.52* (0.41, 0.67)	0.69 (0.40, 1.2)	0.37* (0.14, 0.99)	0.70 (0.23, 2.2)	0.96 (0.38, 2.5)	0.65 (0.36, 1.2)	0.40* (0.28, 0.58)
Direct MD transfer			0.30* (0.22, 0.40)	0.20* (0.11, 0.38)	0.33* (0.13, 0.85)	0.59 (0.21, 1.7)	0.48 (0.14, 1.7)	0.24* (0.09, 0.62)	0.26* (0.15, 0.45)
Walk-in			0.38* (0.27, 0.53)	0.08* (0.02, 0.36)	0.28 (0.07, 1.1)	0.56 (0.08, 3.8)	0.61 (0.18, 2.0)	0.33* (0.14, 0.81)	0.48* (0.31, 0.77)

Note. CI = confidence interval; DxCG = Diagnostic Cost Group; ED = emergency department; MD = physician; OR = odds ratio; pH1N1 = Influenza A.

[a]Model A refers to the null model investigating the association between intensive care unit stay and age group. Model B adds the measure of DxCG score to adjust for comorbidity measure. Model C refers to the full multivariate model investigating the association between intensive care unit stay and age adjusted for DxCG, age, gender, specific risk factors, and source of admission into the hospital.

[b]Omitted.

*$P < .05$.

TABLE 4—Measures of Association Between Influenza-Like Illness–Related Intensive Care Unit Stay and Independent Variables, by Age Among All Discharged Patients Meeting Selection Criteria: Hospital Inpatient Discharge Database, Massachusetts, October 1, 2008–April 25, 2009

Variables	All[a] (n = 7402), OR (95% CI)			< 5 Years (n = 2060), OR (95% CI)	5–12 Years (n = 456), OR (95% CI)	13–18 Years (n = 287), OR (95% CI)	19–25 Years (n = 389), OR (95% CI)	26–44 Years (n = 1413), OR (95% CI)	45–64 Years (n = 2797), OR (95% CI)
	Model A	Model B	Model C						
Age, y									
< 5	0.53* (0.43, 0.65)	1.06 (0.84, 1.3)	1.09 (0.85, 1.4)						
5–12	0.89 (0.65, 1.2)	1.41* (1.0, 2.0)	1.49* (1.1, 2.1)						
13–18	0.90 (0.62, 1.3)	1.41 (0.94, 2.1)	1.48 (0.99, 2.2)						
19–25	0.87 (0.62, 1.2)	1.31 (0.92, 1.9)	1.34 (0.94, 1.9)						
26–44	0.66* (0.53, 0.82)	0.92 (0.73, 1.2)	0.95 (0.76, 1.2)						
45–64 y (Ref)	1.00	1.00	1.00						
DxCG score		1.97* (1.8, 2.2)	1.95* (1.8, 2.1)	3.01* (2.3, 3.9)	2.05* (1.5, 2.9)	3.87* (2.2, 6.7)	2.00* (1.4, 3.0)	2.42* (1.9, 3.0)	1.62* (1.4, 1.8)
Gender									
Female			0.77* (0.66, 0.91)	0.91 (0.63, 1.3)	1.68 (0.89, 3.2)	0.59 (0.25, 1.4)	0.47* (0.23, 0.98)	0.67 (0.45, 1.0)	0.73* (0.58, 0.93)
Male (Ref)			1.00	1.00	1.00	1.00	1.00	1.00	1.00
Race/ethnicity									
Hispanic			0.82 (0.63, 1.1)	1.05 (0.65, 1.7)	0.98 (0.41, 2.4)	0.48 (0.11, 2.1)	0.70 (0.23, 2.2)	0.91 (0.50, 1.7)	0.67 (0.41, 1.1)
Non-Hispanic Black			0.86 (0.65, 1.1)	1.40 (0.79, 2.5)	1.34 (0.58, 3.1)	1.33 (0.39, 4.5)	0.87 (0.30, 2.5)	0.45* (0.21, 0.98)	0.72 (0.46, 1.1)
Other			1.35* (1.1, 1.8)	1.85* (1.2, 3.0)	0.86 (0.28, 2.7)	2.89 (0.72, 11.6)	1.42 (0.44, 4.6)	0.82 (0.33, 2.0)	1.31 (0.77, 2.2)
Non-Hispanic White (Ref)			1.00	1.00	1.00	1.00	1.00	1.00	1.00
Risk factors									
Asthma			1.09 (0.90, 1.3)	1.55* (1.1, 2.3)	1.56 (0.79, 3.1)	2.02 (0.78, 5.2)	0.97 (0.44, 2.1)	0.85 (0.52, 1.4)	0.91 (0.67, 1.2)
Obese			0.74 (0.53, 1.0)	[b]	0.82 (0.09, 7.2)	0.91 (0.10, 8.4)	2.81 (0.70, 11.2)	0.99 (0.51, 1.9)	0.63* (0.41, 0.95)
Pregnant			0.75 (0.32, 1.8)	[b]	[b]	[b]	2.04 (0.57, 7.3)	0.41 (0.09, 1.7)	[b]
Source of admission									
ED transfer			0.56* (0.46, 0.69)	0.70 (0.44, 1.1)	1.14 (0.50, 2.6)	0.67 (0.22, 2.0)	0.75 (0.31, 1.8)	0.58* (0.33, 0.99)	0.49* (0.36, 0.64)
Direct MD transfer			0.36* (0.28, 0.47)	0.32* (0.20, 0.53)	0.40* (0.17, 0.92)	0.21* (0.10, 0.73)	0.64 (0.23, 1.9)	0.68 (0.37, 1.3)	0.31* (0.20, 0.48)
Walk-in			0.50* (0.38, 0.65)	0.30* (0.15, 0.63)	0.11* (0.01, 0.92)	1.38 (0.35, 5.5)	0.64 (0.20, 2.0)	1.04 (0.56, 1.9)	0.45* (0.31, 0.65)

Note. CI = confidence interval; DxCG = Diagnostic Cost Group; ED = emergency department; MD = physician; OR = odds ratio.

[a]Model A refers to the null model investigating the association between intensive care unit stay and age group. Model B adds the measure of DxCG score to adjust for comorbidity measure. Model C refers to the full multivariate model investigating the association between intensive care unit stay and age adjusted for DxCG, age, gender, specific risk factors, and source of admission into the hospital.

[b]Omitted.

*$P < .05$.

groups more severely, causing higher numbers of ICU admissions and fatalities than seasonal influenza. From these results, we can confirm that severe pH1N1 attacked a younger population—but not necessarily a more medically compromised population—with lower comorbidity scores than older populations.

There was a distinct gender distribution by age strata among both the pH1N1 and seasonal influenza groups. Published findings have shown a predominance of male patients among those hospitalized with pH1N1[21] and with severe pH1N1 infection.[22] These differences are also age-dependent, and other work has confirmed higher rates of influenza among female patients of reproductive age. This could indicate a biological predisposition to more severe manifestation of influenza. Published findings have indicated that immunological differences between the sexes may reflect endocrine–immune interactions, and immunity to viruses can vary with changes in hormone concentrations caused by natural fluctuations over the menstrual cycle, contraception use, pregnancy, or menopause,[23] which may explain these gender distributions by age strata.

Asthma was predictive of ILI-related ICU admission among those with seasonal influenza, but results were more dramatic during the pH1N1 time period, indicating that these risk factors were more strongly associated with severe manifestations of pH1N1 infection. We found higher prevalence of asthma among those with pH1N1-related ICU admission than among those with seasonal influenza. Other published findings have shown similar results. In one assessment of children with asthma hospitalized with seasonal and pandemic influenza, a higher proportion of asthmatic children hospitalized with pH1N1 required intensive care than those with seasonal influenza (22% vs 16%).[24]

We found a strong association between women who were pregnant and ICU admission among the pH1N1 cohort. This is consistent with other published findings that have documented the severe effects of pH1N1 on pregnant women.[25,26] One investigation found that nearly half (47%) of pregnant women admitted to the ICU had at least 1 underlying medical condition such as asthma, diabetes, or obesity, indicating that additional risk factors may complicate or exacerbate the course of the disease.[26]

With regard to obesity, there have been mixed measures of association between odds of severe pH1N1 infection and obese individuals in published literature. Some work has shown a strong association between obesity and severe pH1N1.[25] Other work has shown that obesity is not independently associated with pH1N1 hospitalization; however, obesity is associated with other factors that may complicate or exacerbate pH1N1 infection (such as mechanical ventilation).[18] We did not find any statistically significant relationship between those with obesity-related diagnoses and ICU admission among those in the pH1N1 cohort.

Strengths and Limitations

The use of large hospital administrative databases presents an excellent opportunity to explore population-based influenza-associated hospitalizations. Linking plentiful diagnostic HIDD data to the DxCG–HCC model is a novel way to explore predictors of severe influenza during a pandemic. Through the DxCG analysis, we were able to distill thousands of diagnoses into understandable risk scores to compare measures of illness between study populations.

It is possible that noninfluenza medical events could have caused ICU admission among this study population. However, we were not authorized to conduct medical chart abstraction in this study to explore this association further. Population-level attack rates among subpopulations should also be considered during the interpretation of our results.

In addition, data from correctional facilities and veterans' hospitals in Massachusetts are not included in the HIDD. Because the HIDD only includes hospitalization data, we were not able to compare this hospitalized population to nonhospitalized pH1N1 cases to see differences in demographics, diagnoses, or outcomes. We were not authorized to access individual medical chart information; therefore, it was not possible to determine influenza case status for every individual in this study and misclassification is possible.

Conclusions

At the time of writing, this is the first study to report population-based pH1N1-related outcomes by age strata in all statewide acute care centers. This study is an example of the feasibility and utility of linking results from risk analysis software with population-based hospital administrative diagnostic data to describe influenza-related outcomes. We have attempted to uncover the complex interplay among age, comorbidity, and pH1N1-related complications during the 2009 pH1N1 pandemic among all Massachusetts hospitals. We have shown that pH1N1 attacked younger age groups with greater severity, causing hospitalization and admission into the ICU, and even death. We found that those admitted to the ICU during the pH1N1 time period were younger than those with ILI-related ICU admission during the regular influenza season, and had higher prevalence of risk factors shown to complicate or exacerbate pH1N1. Being male was predictive of ILI-related ICU stay. Within the pH1N1 cohort, asthma was highly predictive of ICU admission among those younger than 5 years, 5 to 12 years, and 13 to 18 years, as was pregnancy among those aged 26 to 44 years. Obesity did not predict pH1N1-related ICU admission with any statistical significance.

The implications of our findings lead to the conclusion that high-risk groups such as children younger than 18 years with comorbidities such as asthma, or women who are pregnant, would benefit from improved surveillance and resource allocation during influenza outbreaks. In light of these results, efforts for influenza vaccination and healthy behavior promotion should be focused on high-risk pediatric populations to prevent serious ILI-related complications in these groups during future outbreaks. ■

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Contributors

H. E. D. Placzek participated in the design of the study, performed the statistical analysis, and drafted the article. L. C. Madoff participated in the study design and

coordination and helped to draft the article. Both authors read and approved the final article.

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Human Participant Protection

This project involved retrospective analysis of an administrative hospital database. Institutional review board approval was granted from both UMMS and MDPH Research and Data Access Review Committee.

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