

Severe Influenza in 33 U.S. Hospitals, 2013-2014: Risk Factors for Death in 507 Patients

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Abstract

Background: Influenza A (H1N1) pdm09 became the predominant circulating strain in the U.S. during the 2013-2014 influenza season. Little is known about the epidemiology of severe influenza during this season.

Methods: A retrospective cohort study of severely ill patients in intensive care units (ICUs) in 33 U.S. hospitals between September 2013 and April 2014 was conducted to determine risk factors present on ICU admission for mortality and to describe patient characteristics, spectrum of disease, management and outcomes.

Results: 444 adults and 63 children were admitted to an ICU in a study hospital; 93 (20.9%) adults and 4 (6.4%) children died. By logistic regression analysis, older age (> 65 years, OR 3.1 [1.4-6.9], p = 0.006 and 50-64 years, OR 2.5 [1.3-4.9], p = 0.007; reference age 18-49), male sex (OR 1.9 [1.1-3.3], p = 0.031), history of malignancy with chemotherapy administered within the prior 6 months (OR 12.1 [3.9-37.0], p < 0.001) and a higher Sequential Organ Failure Assessment (SOFA) score (for each increase by 1 in SOFA score, OR 1.3 [1.2-1.4], p < 0.001) were significantly associated with mortality among adult patients.

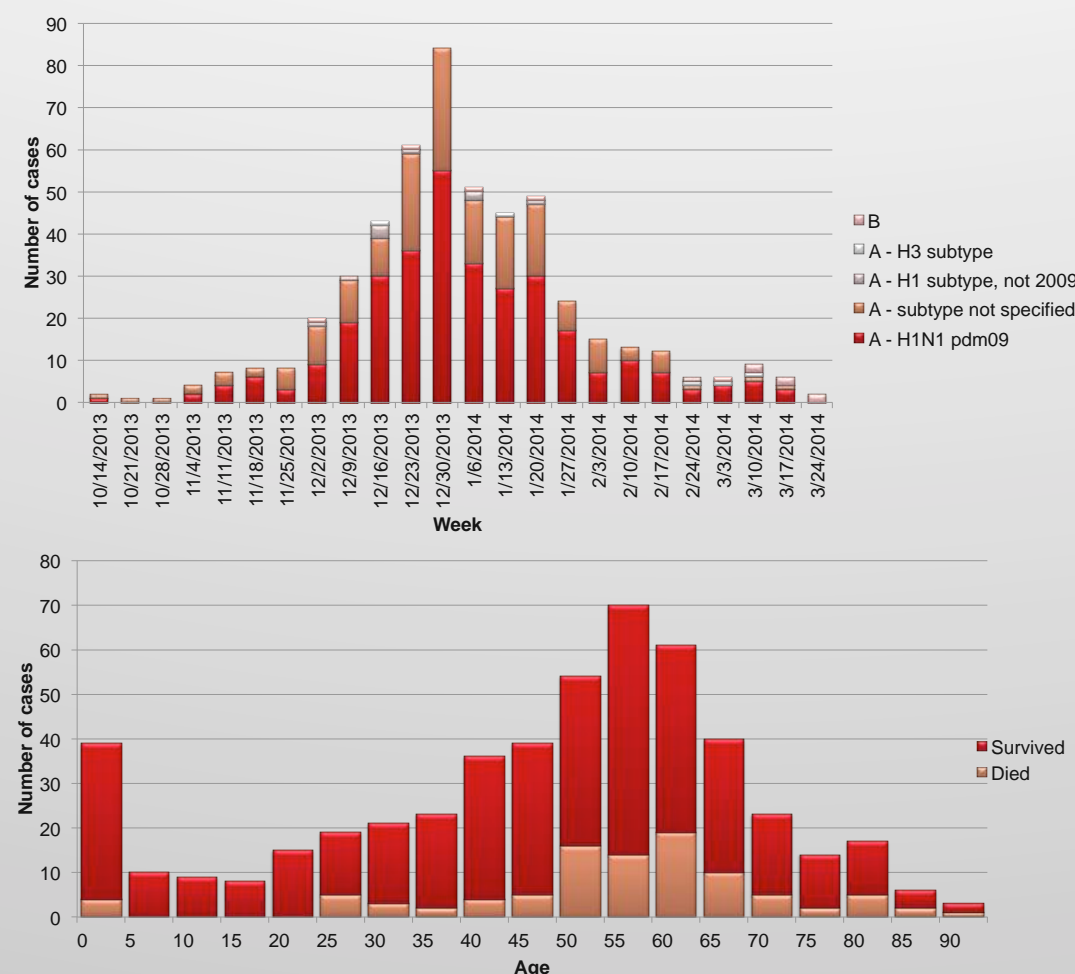
Conclusions: Risk factors for death among U.S. patients with severe influenza during the 2013-2014 season, when influenza A (H1N1) pdm09 was the predominant circulating strain type were similar to risk factors traditionally associated with usual epidemic influenza seasons.

Background

- Influenza kills an estimated 30,000 to 49,000 people in the U.S. each year.
- Influenza occurs in epidemics in the U.S. each winter.
- Every century there are two to six pandemics, when a novel strain type of influenza A emerges, spreads rapidly and becomes the predominant circulating strain.
- Influenza A (H1N1) pdm09 emerged in the 2009 pandemic year
- After 2009, the novel influenza A (H1N1) pdm09 virus did not become the exclusive circulating influenza A strain until the 2013-2014 season in the U.S.
- During normal epidemic influenza seasons, the majority of deaths occur in young children and in adults > 65 years of age.
- In pandemics a great number of deaths occur in young adults as was seen in the 2009 pandemic season
- It is not known whether the patient population at risk for severe illness and death during 2013-2014 was similar to the 2009-2010 season.

Methods

- Thirty three study hospitals participated in the Severe H1N1 Influenza Consortium 2014 (SHIC 2014).
- Retrospective cohort study
- Subjects included all patients who tested positive for influenza and were admitted to an ICU during the influenza season (September 1, 2013 to April 1, 2014).
- The patient must have been diagnosed with laboratory confirmed influenza during an ICU stay or within 30 days prior to ICU admission.
- Data were abstracted from the hospital's electronic health record and entered into a REDCap
- Patient specific and site specific data were collected
- Outliers were reexamined in the electronic medical record to ensure that data were accurate. No subjects with outlying values were dropped from any analysis.
- Bivariable analyses were performed to compare potential risk factors for death within 30 days of ICU admission.
- A multivariable logistic regression model was developed to determine which of the variables significantly associated in bivariable analyses at a p < 0.05 were statistically associated with death.
- In four sensitivity analyses, we ran the model without the SOFA score, only with influenza A (H1N1) pdm09 cases, excluding centers that used non PCR based diagnostic assays and excluding patients who were diagnosed with influenza greater than 7 days prior to ICU admission.



Characteristics ^a	Adults (N=444) No. (%)	Pediatrics (N=63) No. (%)	
Sex	Female 223 (50.2)	28 (44.4)	
Age group	0-23 mo	27 (5.3)	
	2-4 yr	12 (2.4)	
	5-9 yr	10 (2.0)	
	10-17 yr	14 (2.8)	
	18-49 yr	156 (30.8)	-
	50-64 yr	185 (36.5)	-
Body mass index kg/m ²	< 30	103 (20.3)	
	30-39 (obese)	233 (52.4)	
	≥ 40 (morbidly obese)	142 (32.0)	
	Unknown	71 (16.0)	
Pregnancy (N = 251)	Currently pregnant	10 (4.7)	
	A - H1N1 pdm2009	274 (61.7)	
	A - subtype not specified	150 (33.8)	
Influenza type and subtype	A - H1 subtype not pdm2009	6 (1.4)	
	A - H3	3 (0.7)	
	B	11 (2.5)	
	Other	7 (1.6)	
Initial influenza diagnostic test (N=506)	Polymerase chain reaction	369 (83.1)	
	Rapid influenza test	61 (13.7)	
	Viral culture	7 (1.6)	
Exposures	Known health care exposure in the previous 12 mo (N=370)	150 (47.3)	
	Recorded sick contact (N=505)	100 (22.6)	
	Symptoms onset > 48 hr after hospital admission (N=502)	24 (5.5)	
	Received 2013-14 vaccine (N=258)	108 (51.4)	
Vaccines	Received 2013-14 vaccine ≥ 14 days prior to symptom onset (N=229)	58 (31.5)	
	Bloodstream infection on admission	23 (5.2)	
	Received after symptom onset	421 (94.8)	
Coinfections	Initiated prior to hospitalization (N=478)	153 (36.3)	
	Initiated ≤ 48 hr after symptom onset (N=474)	110 (26.4)	
	Present	413 (93.0)	
ACIP preexisting condition	> 7	14 (3.2)	
	0-7	294 (66.2)	
	Diagnosed after ICU admission	136 (30.6)	
Died		93 (20.9)	

Legend

Figure 1 (Left upper): 507 patients with influenza admitted to intensive care units at 33 U.S. hospitals, by week, between October 1, 2013 and April 1, 2014, indicating influenza type and subtype.

Figure 2 (Left middle): Age distribution of 507 patients with severe influenza infection in the U.S. between September 1, 2013 and April 1, 2014, by outcome.

Table 1 (Right): Characteristics of 507 patients with severe influenza infection in the U.S. diagnosed between September 1, 2013 and April 1, 2014, comparing adult and pediatric patients.

Table 2 (Left lower): Patient characteristics associated with mortality among 444 adult patients with severe influenza infection in the U.S. between September 1, 2013 and April 1, 2014: Results of bivariable analyses and a multivariable logistic regression model.

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Results

- 507 patients (444 adults and 63 children) with influenza infection were admitted to an ICU at the 33 study hospitals
- 311 (61.3%) infections were Influenza A (H1N1) pdm09, 170 (33.5%) infections were influenza A but were not subtyped, 8 (1.6%) were influenza A with an H1 subtype other than pdm09, 5 (1.0%) were influenza A with an H3 subtype and 13 (2.6%) were influenza B
- Characteristics associated with mortality among adults included
 - **older age** (> 65 years, OR 3.1 [95% CI, 1.4-6.9], p = 0.006 and 50-64 years, OR 2.5 [1.3-4.9], p = 0.007; reference group 18-49 years),
 - **male sex** (OR 1.9 [1.1-3.3], p = 0.031),
 - **history of malignancy with chemotherapy administered within the prior six months** (OR 12.1 [3.9-37.0], p < 0.001)
 - **higher SOFA score** (for each increase by 1 in SOFA score, OR 1.3 [1.2-1.4], p < 0.001).
- 3 sensitivity analysis showed no change in the variables significantly associated with death. These regression models were
 - 1) excluding patients infected with influenza B, influenza A of an H3 subtype or Influenza A of an H1 subtype other than pdm09
 - 2) excluding centers that utilized only rapid influenza tests
 - 3) excluding patients diagnosed greater than 7 days prior to ICU admission
- When SOFA score was excluded two additional covariates becoming significantly associated with death: 1) having infiltrates on initial chest x-ray in ≥2 lung quadrants and 2) having been admitted to a hospital, a skilled nursing facility or a long-term extended care facility during the prior year.

Conclusion

- Risk factors on admission to an ICU that increased the likelihood of death among adult patients with severe influenza during 2013-2014 included: older age, male gender, history of recent chemotherapy administration and an elevated SOFA score.
- We did not find associations with previously described risk factors for death among those infected with influenza A H1N1 pdm09 virus in 2009.
- Our findings suggest that risk factors associated with death from severe illness caused by influenza A H1N1 pdm09 virus may have shifted in this first predominant influenza A H1N1 pdm09 postpandemic season

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Characteristic ^b	Survived; N=351 (%)	Deceased; N=93 (%)	Bivariable; P value	Multivariable; odds ratio (95% CI), P value	
Age, years	18-49	137 (39.0)	19 (20.4)	Reference	
	50-64	136 (38.8)	49 (52.7)	2.5 (1.3-4.9), p=0.007	
	> 65	78 (22.2)	25 (26.9)	3.1 (1.4-6.9), p=0.006	
	Reference				
Sex	Female	188 (53.6)	35 (37.6)	Reference	
	Male	163 (46.4)	58 (62.4)	1.9 (1.1-3.3), p=0.031	
Body mass index, kg/m ² (N=439)	< 30	184 (52.4)	49 (55.7)	0.30	
	30-39 (obese)	119 (33.9)	23 (26.1)		
	≥ 40 (morbidly obese)	48 (13.7)	16 (18.2)		
Documented sick contact (N=442)	87 (24.9)	13 (14.1)	0.029	0.79 (0.37-1.7), p=0.53	
Admission to a hospital or SNF/LTEC stay in the prior year	Yes	111 (31.6)	39 (41.9)	Reference	
	No	144 (41.0)	23 (24.7)	0.58 (0.29-1.2), p=0.12	
	Unknown	96 (27.4)	31 (33.3)	0.69 (0.35-1.4), p=0.28	
Comorbidities	Asthma	71 (20.2)	10 (10.8)	0.035	0.62 (0.26-1.5), p=0.27
	COPD or other chronic lung disease (N=443)	123 (35.1)	27 (29.0)	0.27	
	Cardiovascular disease	102 (29.1)	27 (29.0)	0.99	
	Diabetes mellitus	110 (31.3)	29 (31.2)	0.98	
	Chronic kidney disease	57 (16.3)	15 (16.1)	0.96	
	Liver disease	19 (5.4)	10 (10.8)	0.064	
	Malignancy, received chemotherapy in past 6 mo	10 (2.9)	17 (18.3)	<0.001	12.1 (3.9-37.0), p<0.001
	HIV infection	7 (2.0)	2 (2.2)	0.92	
	Dementia	12 (3.4)	2 (2.2)	0.53	
	Other neurologic diseases	40 (11.4)	9 (9.7)	0.64	
	History of transplant	24 (6.8)	12 (12.9)	0.057	
	Received steroid and/or biologic within the past month (N=443)	31 (8.8)	8 (8.7)	0.97	
FTT or malnutrition (N=443)	13 (3.7)	5 (5.4)	0.47		
Current smoker (N=442)	110 (31.4)	21 (22.8)	0.11		
No PMH (N=438)	68 (19.6)	13 (14.3)	0.25		
ACIP comorbid condition ^c	324 (92.3)	89 (95.7)	0.25		
Coinfection	Coinfection with viral respiratory pathogen within 48 hr of admission (N=441)	5 (1.4)	5 (5.4)	0.023	2.7 (0.56-13.1), p=0.21
	Bacteremia on admission ^d	15 (4.3)	8 (8.6)	0.094	
	Respiratory tract infection on admission ^{d,e}	31 (8.8)	14 (15.1)	0.077	
Antiviral therapy (N=417)	Antiviral administered within 48 hr of symptom onset	92 (27.7)	18 (21.2)	0.22	
	Vaccine ≥ 14 d prior to symptom onset (N=189)	51 (31.3)	12 (46.2)	0.14	
White blood cell count, K/uL (N=443)	Yes	112 (68.7)	14 (53.9)	Reference	
	No	124 (35.3)	30 (32.6)		
	> 11 (Leukocytosis)	200 (57.0)	47 (51.1)	0.043	1.1 (0.57-2.0), p=0.86
	3.5-11 (Normal)	27 (7.7)	15 (16.3)		0.65 (0.23-1.9), p=0.42
SOFA score; mean (sd) (N=440) ^f	≥ 2	173 (49.3)	60 (64.5)	0.009	1.3 (1.2-1.4), p<0.001
	≥ 12 (high PEEP group)	41 (24.9)	17 (21.3)	0.53	
	< 8 ml/kg of ideal body weight	82 (82.8)	44 (88.0)	0.41	