

Influenza pneumonia among adolescents and adults: a concurrent comparison between influenza A (H1N1) pdm09 and A (H3N2) in the post-pandemic period

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Abstract

Introduction: Comparisons of the characteristics between the influenza A (H1N1) pdm09 and common seasonal influenza are important for both clinical management and epidemiological studies. However, the differences between pandemic and seasonal influenza during the post-pandemic period are poorly understood.

Objectives: The aim of our research was to investigate clinical and immune response differences between patients with influenza A (H1N1) pdm09 pneumonia and seasonal influenza A (H3N2) pneumonia in the post-pandemic period.

Methods: During the first flu season in post-pandemic period, patients from Beijing Network for Adult Community-Acquired Pneumonia present A (H1N1) pdm09 or A (H3N2) influenza were compared concurrently in the aspects of clinical characteristics and inflammatory profile in acute phase.

Result: Patients with A (H1N1) pdm09 influenza pneumonia showed a close mean age to A (H3N2) pneumonia (51 ± 20 vs 53 ± 16 , mean \pm standard deviation, years) but tended to have more underlying diseases (32.8% vs 10%, $P = 0.036$). Although clinical characteristics were similar, no statistical difference were found in pneumonia severity index (PSI) score or intensive care unit admission rate or mortality, patients in A (H1N1) pdm09 cohort present higher levels of aspartate aminotransferase, lactate dehydrogenase ($P = 0.006$, 0.018 , respectively) in blood and also longer duration of fever than A (H3N2) cohort. Levels of interleukin (IL)-10 and IL-12 (p70) were higher in A (H1N1) pdm09 cohort ($P = 0.031$, 0.047 , respectively).

Conclusions: During the first post-pandemic flu season, patients with the A (H1N1) pdm09 pneumonia showed similar clinical characteristics but slightly higher disease severity and stronger systemic inflammatory response than A (H3N2) pneumonia.

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Key words

influenza A (H1N1) pdm09 – pneumonia – post-pandemic – seasonal influenza A (H3N2)

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Authorship and contributorship

Chen Wang and Bin Cao designed the study. Xiao Min Yu and Ying Mei Liu collected data. Shu Qiao Yang and Jiu Xin Qu performed the study and wrote the paper.

Ethics

This research was approved by institutional review board in Beijing Chao-Yang Hospital. All patients gave their informed consents.

Conflict of interest

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Introduction

In 2009, a novel influenza A (H1N1) pdm09 caused outbreaks of respiratory illness in southern America and reached nearly every country in the world within several weeks (1). As of August 2010, more than 214 countries had reported laboratory-confirmed cases resulting a total number over 18 449 death (2). Early published data during pandemic have shown that infection and serious illnesses occurred mostly in children and young adults, which differed significantly from seasonal influenza (3, 4).

During pandemic in 2009, Kelvin KW To and coauthors demonstrated that pandemic A (H1N1) patients were younger, less likely to have lower respiratory tract symptoms, more likely to be obese or pregnant (5) compared with seasonal influenza. Nelson Lee *et al.* also proved that hospitalized patients with A (H1N1) pdm09 influenza were younger than those with seasonal influenza and had higher rates of extrapulmonary complications and intensive care unit (ICU) admission and/or death (6). Susanna Esposito *et al.* (7) showed symptom severity and the risk of serious outcomes (admission to ICU or death) were similar in children because of pandemic H1N1 or seasonal A (H3N2).

But the main limitation of these studies is that comparison was made during pandemic, as it is easily understood when a new subtype of influenza virus was introduced into the community. When A (H1N1) pdm09 virus has been circulating and became an endemic causative respiratory pathogen during post-pandemic, it is unclear whether the A (H1N1) pdm09 has some difference from pre-existing influenza A (H3N2).

During the immediate post-pandemic period, a surveillance network (Beijing Network for Adult Community-Acquired Pneumonia, BNACAP), comprising 12 general hospitals in Beijing, was established to survey community-acquired pneumonia (CAP) cases in Beijing district. Such survey offered a unique opportunity to study the behavior of A (H1N1) pdm09 influenza during the immediate post-pandemic phase and perform a concurrent comparison between A (H1N1) pdm09 influenza pneumonia and seasonal influenza A (H3N2) pneumonia. Cytokine dysregulation may contribute to lung pathology and severity of influenza A virus infection (8). Another novelty of this study is that we also compared the immune response between the two kinds of pneumonia.

Materials and methods

Study population

During November 2010 and April 2011, the first flu season in post-pandemic period, adolescent and adult patients (aged 14 years or above) with chest radiograph confirmed CAP from 12 general hospitals were consecutively enrolled in BNACAP. Patients were excluded if they met any of the following items: time before enrollment since disease onset >7 days, immunocompromised patients with human immunodeficiency virus infection, neutropenia, receiving immunosuppressive chemotherapy, pregnant or breastfeeding women, and known or suspected active tuberculosis.

Data collection and microbiology diagnosis

Epidemiological data, symptoms and signs, laboratory findings on admission, clinical course, treatment, and outcomes were recorded. The pneumonia severity index (PSI) was used to assess the severity of illness (9).

Throat swab specimens, sputum, serum and urine were collected on admission. Throat swabs were performed with 2-mL transport broth medium (CM403, OXOID, Basingstoke, Hampshire, UK) and stored at -80°C until transportation on ice to the central laboratory in Beijing Chao-Yang Hospital within 2 weeks. Multiplex polymerase chain reaction (PCR) assay (RV15 ACE Detection, Seegene, Inc., Seoul, Korea) were used to detect influenza virus and other 14 kinds of common respiratory pathogens. Samples confirmed with influenza virus infected were subsequently discriminated for subtypes by real-time, reverse transcriptase (RT) PCR assay [Diagnostic Kit for seasonal influenza A subtype H3 and H1 virus RNA; Diagnostic Kit for pandemic influenza A (H1N1) virus RNA, Kinghawk, Inc., Peking, China]. Blood cultures were performed for patients presenting with chills and shivering. If pleural fluid and sputum samples were available, Gram stain and quantitative culture were performed. The sputum sample was determined to be adequate if >25 polymorphonuclear cells and <10 epithelial cells were counted per high power field. Urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* (BinaxNow[®] *S. pneumoniae* and BinaxNow *Legionella*, Scarborough, ME, USA) were also performed.

Cases of A (H1N1) pdm09 virus or seasonal H3N2 virus infection were defined when RT-PCR assay present positive results. Bacteria coinfection was considered if etiology were detected by culture or Gram stain, or urinary antigen tests.

Cytokines and chemokines quantification

Cytokine and chemokine levels were evaluated by using the multiplex Biorad 27plex assay (Hercules, CA, USA) in serum of acute phase, if available, for healthy volunteers and patients with pandemic influenza A (H1N1) virus or seasonal influenza virus infection. The kit was customized to quantify 20 kinds of cytokines and chemokines in serum, including interleukin (IL)-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, eotaxin, interferon (IFN)- γ , IFN gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), regulated on activation, normal T-cell expressed and secreted (RANTES), and tumor necrosis factor (TNF)- α .

Statistical analysis

SPSS 17.0 was utilized to perform data analysis. Two-tailed independent samples *t*-test or Mann–Whitney *U*-test (on condition of non-normal distributions) was conducted to compare continuous variables between two groups. As for the categorical data, univariate analysis was carried out using the chi-square test or Fisher's exact test. Measurement data are displayed as mean \pm standard deviation (SD), or as median (interquartile rank) when data were not normally distributed. Numeration data are presented in numbers (%). Significance was fixed at *P* value <0.05 .

Results

Epidemiological data

There were 92 patients presenting influenza A infection, 62 with A (H1N1) pdm09 influenza and 34 with seasonal influenza (H3N2), among them, four were coinfecting with both of the two kinds of virus and thus were excluded. Acute phase serum was successfully collected from 55 cases [31 A (H1N1) pdm09 influenza and 24 influenza A (H3N2)] and 14 healthy volunteers for examination of the cytokine and chemokine profile.

Clinical characteristics and clinical outcome comparison

Comparison between clinical characteristic of patients with A (H1N1) pdm09 influenza pneumonia and seasonal influenza (H3N2) pneumonia are detailed in Table 1.

The mean ages between the two groups were close (51 ± 20 vs 53 ± 16 , mean \pm SD, years), no statistical difference was found. Patients with A (H1N1) pdm09 influenza pneumonia were more likely to have underlying diseases than those with seasonal influenza (H3N2) pneumonia (32.8% vs 10%, $P=0.036$). A smoking history and antibiotic treatment before enrollment were common in both groups, whereas the ratio of influenza vaccination was rather low (8.0%).

Symptoms and signs were similar in the two groups. Fever and cough were the most frequent symptoms, while the most common sign was moist rales. In comparison with H3N2 cohort, serum levels of aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) in A (H1N1) pdm09 cohort were significantly higher ($P=0.006$, 0.018 , respectively), whereas albumin was significantly lower ($P<0.001$).

Hospitalization rate in A (H1N1) pdm09 cohort was higher (81% vs 56.7%, $P=0.023$). The duration of hospitalization did not differ obviously, but the duration of fever was longer in A (H1N1) pdm09 cohort ($P=0.035$). All the patients were treated with antibiotic after enrollment, whereas only 15 patients (17.0%), all in A (H1N1) pdm09 cohort, were given antiviral treatment. Totally, two patients with A (H1N1) pdm09 influenza pneumonia developed severe complications. One was an 89-year-old man with cerebrovascular diseases; he developed acute respiratory distress syndrome (ARDS) and died quickly. The other one was female, 75 years old, with coronary heart diseases and diabetes; she also developed ARDS but survived.

Cytokine and chemokine data

Increased serum concentrations of inflammatory cytokines and chemokines, including IL-1ra, IL-4, IL-6, IL-7, IL-8, RANTES and eotaxin, were observed in both groups when compared with normal control group ($P<0.05$). Moreover, statistically significant higher levels of IL-10 and IL-12 (p70) were found in A (H1N1) pdm09 group in comparison with seasonal influenza (H3N2) group ($P=0.031$, 0.047 , respectively). Cytokine and chemokine profile were shown in Fig. 1.

Discussion

Data from this study present similar clinical characteristics but still a slightly higher disease severity in patients between A (H1N1) pdm09 influenza pneumonia during post-pandemic period, when concurrently compared with seasonal influenza (H3N2) pneumonia.

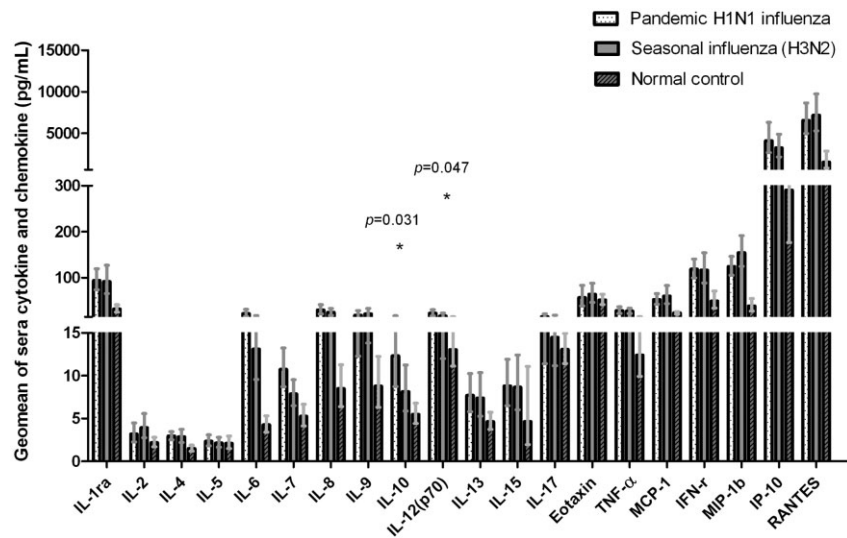
Table 1. Clinical characteristics of patients with A (H1N1) pdm09 influenza pneumonia and seasonal influenza (H3N2) pneumonia

	Total (N = 88)	A (H1N1) pdm09 (n = 58)	A (H3N2) (n = 30)	P value
Basic statistics				
Male	48 (54.5%)	34 (58.6%)	14 (46.7%)	0.29
Age (years)	52 ± 19	51 ± 20	53 ± 16	0.70
Underlying diseases	22 (25%)	19 (32.8%)	3 (10%)	0.019
COPD	9 (10.2%)	7 (12.1%)	2 (6.7%)	0.67
Diabetes	6 (6.8%)	6 (10.3%)	0	–
Coronary heart diseases	7 (8.0%)	5 (8.6%)	2 (6.7%)	1.0
Cerebrovascular diseases	5 (5.7%)	5 (8.6%)	0	–
Chronic heart diseases	1 (1.1%)	1 (1.7%)	0	–
Chronic renal diseases	2 (2.3%)	2 (3.4%)	0	–
Cirrhosis	2 (2.3%)	2 (3.4%)	0	–
Smoking history	24 (27.3%)	16 (27.6%)	8 (26.7%)	1.0
Influenza vaccination within 1 year	7 (8.0%)	7 (12.1%)	0	–
<i>Streptococcus pneumoniae</i> vaccination within 1 year	2 (2.3%)	2 (3.4%)	0	–
Antibiotics before enrollment	53 (60.2%)	32 (55.2%)	21 (70.0%)	0.25
Symptoms and signs on admission				
Fever	85 (96.6%)	57 (98.3%)	28 (93.3%)	0.55
Tmax (°C)	38.9 (38.8–39.1)	38.9 (38.8–39.1)	38.9 (38.6–39.3)	0.65
Cough	85 (96.6%)	56 (96.6%)	29 (96.7%)	1.0
Expectoration	72 (81.8%)	47 (81.0%)	25 (83.3%)	1.0
White sputum	38 (53.5%)	24 (52.2%)	14 (56.0%)	0.81
Yellow sputum	30 (42.3%)	20 (43.5%)	10 (40.0%)	0.81
Bloody sputum	3 (4.2%)	2 (4.3%)	1 (4.0%)	1.0
Dyspnea	25 (28.4%)	17 (29.3%)	8 (26.7%)	0.81
Chest pain	9 (10.2%)	7 (12.1%)	2 (6.7%)	0.67
Nausea or vomiting	6 (6.8%)	3 (5.2%)	3 (10.0%)	0.69
Headache or dizziness	11 (12.5%)	6 (10.3%)	5 (16.7%)	0.61
Confusion	0	0	0	–
Respiratory rate (/min)	20 (19.7–21.1)	20 (19.8–21.7)	20 (19.1–20.3)	0.25
Systemic blood pressure (mmHg)	120 (119–125)	120 (119–127)	120 (116–126)	0.90
Conjunctival congestion	3 (3.4%)	2 (3.4%)	1 (4.3%)	1.0
Moist rales	38 (43.2%)	25 (43.1%)	13 (43.3%)	1.0
Dry rales	20 (22.7%)	17 (29.3%)	3 (10.0%)	0.06
Skin rash	1 (1.1%)	1 (1.7%)	0	–
PSI score	53.4 ± 26.2	56.0 ± 29.4	48.0 ± 17.2	0.13
Laboratory findings on admission				
WBC (×10 ⁹ /L)	6.9 ± 2.9	7.3 ± 2.9	6.4 ± 2.7	0.16
Lymphocytes (×10 ⁹ /L)	1.1 ± 0.5	1.1 ± 0.5	1.1 ± 0.5	0.74
Hemoglobin (g/L)	133.6 ± 19.5	132.7 ± 22.3	135.1 ± 13.2	0.58
Platelet (×10 ⁹ /L)	190.8 ± 70.2	189.9 ± 71.1	192.4 ± 69.8	0.87
Abnormal ECG	20 (22.7%)	16 (27.6%)	4 (13.3%)	0.13
ALT (U/L)	21 (22.1–31.1)	22 (22.5–35.7)	18 (17.9–26.3)	0.39
AST (U/L)	24.4 (25.2–33.8)	27 (27.2–39.8)	20 (19.5–25.0)	0.006
ALB (g/L)	37.1 ± 5.9	35.3 ± 5.9	40.3 ± 4.1	<0.001
LDH (U/L)	182.5 (187.3–219.6)	201 (198.6–242.8)	175 (154.6–189.5)	0.018
CK (U/L)	90 (105.4–172.9)	89 (110.2–191.2)	91 (55.1–180.9)	0.32
Cr (μmol/L)	71.1 ± 19.9	71.9 ± 19.5	71.6 ± 13.1	0.93
ESR (mm/h)	24.5 (9.8–43.5)	25 (10.8–43.5)	17 (5.5–47.5)	0.26
CRP (mg/L)	14.6 (6.2–48)	14.2 (6.0–50)	15.4 (9.8–44.6)	0.53
Treatment and outcomes				
Hospitalization	64 (72.7%)	47 (81.0%)	17 (56.7%)	0.015
ICU admission	1 (1.1%)	1 (1.7%)	0/30	–
Antiviral therapy	15 (17.0%)	15 (25.9%)	0/30	–
Antiviral within 48 h onset	1 (1.1%)	1 (1.7%)	0	–
Antibiotics after enrollment	88 (100%)	58 (100%)	30 (100%)	–
Oxygen therapy	38 (43.2%)	27 (46.6%)	11 (36.7%)	0.49
Noninvasive ventilation	4 (4.5%)	4 (6.9%)	0	–
Invasive ventilation	1 (1.1%)	1 (1.7%)	0	–
Vasoactivating agents	2 (2.3%)	1 (1.7%)	1 (3.3%)	1.0
Secondary bacterial infections	9 (14.3%)	3 (7.7%)	6 (25.0%)	0.13
Complications				
ARDS	2 (2.3%)	2 (3.4%)	0	–
Shock	1 (1.1%)	1 (1.7%)	0	–
Empyema	0	0	0	–
Acute renal failure	0	0	0	–
Duration of hospitalization (ds)	7 (5–11)	7 (5–11)	8 (6–10)	0.59
Duration of fever (ds)	5 (4–7)	6 (4–8)	4 (4–6)	0.035
Duration of cough (ds)	15 (10–25)	15 (10–27)	15 (9.8–21)	0.43
Duration of sputum (ds)	14 (9–23)	15 (8.5–28)	14 (9.3–20)	0.59
Duration of dyspnea (ds)	8 (3–10.5)	7.5 (3–10.3)	8 (1–12)	0.59
Death	1 (1.1%)	1 (1.7%)	0	–

Measurement data are displayed as mean ± standard deviation, or as median (interquartile rank) when data were not normally distributed, numeration data are presented in numbers (%).

COPD, chronic obstructive pulmonary disease; PSI, pneumonia severity index; WBC, white blood cell; Hb, hemoglobin; ECG, electrocardiogram; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; CK, creatinine kinase; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PT, prothrombin time; ARDS, acute respiratory distress syndrome; PSI, pneumonia severity index. Bold values indicate statistical significance.

Figure 1. Comparison of cytokine and chemokine profile among patients with pandemic 2009 influenza A pneumonia and seasonal influenza A (H3N2) pneumonia. Statistically significant higher levels of interleukin (IL)-10 ($P = 0.031$) and IL-12 (p70, $P = 0.047$) were found in A (H1N1) pdm09 group in comparison to seasonal influenza (H3N2) group. IFN, interferon; IP-10, IFN gamma-induced protein 10; MCP-1, monocyte chemoattractant protein-1; MIP-1, macrophage inflammatory protein 1; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor.



As in the pandemic period, studies have reported a younger age and fewer comorbid conditions in adult patients with A (H1N1) pdm09 influenza than seasonal influenza, and this was supposed to result from a lack of cross-reactive antibody toward A (H1N1) pdm09 in the younger population (5, 6, 10). On the 10th of August, World Health Organization announced that 2009 pandemic had 'largely run its course', the A (H1N1) pdm09 influenza entered the post-pandemic period. Based on available evidence and experience from past pandemics, the virus was expected to take on the behavior of a seasonal influenza virus (11). In the post-pandemic phase, an upward shift in age distribution of patients infected with A (H1N1) pdm09 virus was reported (12–14). In our study, we also detected a close mean age between patients with A (H1N1) pdm09 influenza pneumonia and seasonal influenza (H3N2) pneumonia, considering the A (H1N1) pdm09 virus has already been reported to remain genetically stable with no increase in virulence since its origin (15); this upward shift in age distribution is probably due to a higher seropositivity against A (H1N1) pdm09 virus in young adult patients.

During the pandemic period, data from Lee *et al.* (6) indicated that patients with A (H1N1) pdm09 influenza have higher rates of extrapulmonary complications, and ICU admission and/or death than seasonal influenza. Riquelme *et al.* (16) conducted a comparison between A (H1N1) pdm09 influenza pneumonia and seasonal influenza (H3N2) pneumonia, rate of ICU admission and mechanical ventilation were found to be higher, and mortality was twice as high in the group of A (H1N1) pdm09 influenza. However, this

study used historical data for comparison, thus potential biases may arise. In our study, although the mean ages were close, symptoms and signs were similar; the rate of ICU admission and death did not differ obviously; and significantly higher serum levels of both AST and LDH, higher rate of hospitalization, and longer duration of fever were found in influenza A (H1N1) pdm09 cohort. The elevation of AST and LDH in blood usually indicate the damage of muscle or organ, which, has been found to be higher in severe patients with A (H1N1) pdm09 virus infection than nonsevere patients (17).

Measurement of cytokines in plasma revealed elevated levels of IL-10 and IL-12 in A (H1N1) pdm09 compared with A/H3N2. IL-10 acts as a major immunomodulatory cytokine. It can inhibit antigen-presenting cells and macrophage function, suppress Th1 cytokine production, and impair T-cell responses (18). Increased production of IL-10 probably reflects a host response to dampen over-exuberant pulmonary inflammation and promote tissue repair (19). IL-12 appears to be important primarily in early activation of the immune response during primary influenza virus infection. IL-12 contributes to the inhibition of early virus replication but is not required for virus clearance. IL-12 also modestly contributes to the activation of cytotoxic T lymphocytes (20). Higher levels of IL-10 and IL-12 (p70) in A (H1N1) pdm09 group in comparison with H3N2 group may indicate a slightly stronger systemic inflammatory response.

The stronger systemic inflammatory response in A (H1N1) pdm09 was supported by animal model by Itoh *et al.* (19). They found that infection with A/Kawasaki/UTK-4/09 resulted in limited induction of pro-

inflammatory cytokines/chemokines in the lungs in marked contrast with infection with A (H1N1) pdm09.

But Österlund *et al.* (21) reported a poor pro-inflammatory cytokine gene expression in human monocyte-derived dendritic cells and macrophages infected with A (H1N1) pdm09. Woo *et al.* (22) also documented that no major cytokine storm, as in H5N1 infection, is associated with A (H1N1) pdm09 infection. Janina Geiler *et al.* (23) even demonstrated that pandemic H1N1/2009 increased IP-10, TNF- α , CXCL8 (interleukin 8 [IL-8]), macrophage inflammatory protein 1 α and IL-6 expression to a lesser extent than H5N1/2004 or H3N2/2004.

The difference might be due to the sample types and viral load between these studies and ours. First, compared with animal or *in vitro* immunocytes infection model, our study is the only clinical trial. Even for clinical trials, the severity of illness or sera collection time after infection might also contribute the difference. Second, the apparent difference between these *in vitro* data reflects different viral loads used in these studies (22). The plasma levels of IP-10, MCP-1, IL-8, IL-6 and IL-10 correlated with pharyngeal H5N1 load (23).

There are several limitations of our study. First, a relatively small sample size may limit the statistical power. Second, only adolescent and adult patients were included; therefore, the findings cannot be generalized to the whole population. Third, the obvious higher proportions of patients with underlying diseases like chronic obstructive pulmonary disease in the pH 1N1 cohort may result in influenza A (H1N1) pdm09 infection more severe than H3N2 infection.

In conclusion, during the first post-pandemic flu season, patients with influenza A (H1N1) pdm09 pneumonia showed similar clinical characteristics but slightly higher disease severity and stronger systemic inflammatory response than seasonal influenza A (H3N2) pneumonia.

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