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Original Article

# Clinical epidemiology comparison of H1N1 RT-PCR-positive and RT-PCR-negative pneumonia during the 2009–2010 pandemic in Mansoura University Hospitals, Egypt

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**Background** Worldwide, the infectivity and disease burden of the H1N1 pandemic were overestimated because of limited clinical experience concerning patient presentation and outcome of those infected with the novel H1N1 virus.

**Objective** This study aimed to compare the epidemiologic clinical data among H1N1 RT-PCR-positive and RT-PCR-negative pneumonic patients during the 2009–2010 pandemic in Mansoura University Hospitals, Egypt.

**Methods** A record-based, case–control study was conducted for 43 adult patients admitted to the chest department isolation unit with community-acquired pneumonia during the 2009–2010 H1N1 pandemic after reviewing of 198 suspected and confirmed H1N1 hospitalized cases. Of these patients, 20 cases were confirmed to be H1N1-positive using an RT-PCR detection technique. The remaining 23 patients were RT-PCR-negative. Demographic, clinical, laboratory and radiological data were collected and analyzed using SPSS version 11.

**Results** A review of 198 hospital case records for revealed one main peak of H1N1 influenza during the last week of December 2009. Pneumonic patients who were H1N1-positive were more likely to present with sore throat ($P = 0{\cdot}005$), dyspnea ($P = 0{\cdot}002$), and gastrointestinal (GIT) complaints (vomiting and diarrhea $P = 0{\cdot}02$) when compared to the H1N1-negative group. Also, complications were significantly more frequent ($P = 0{\cdot}01$) in the H1N1-confirmed group than in the non-confirmed group. However, no significant differences were found between the groups regarding length of hospital stay, intensive care unit (ICU), and admission or mortality.

**Conclusion** Sore throat, dyspnea, and presence of GIT complaints increase the suspicion of H1N1 positivity in pneumonia acquired during an H1N1 pandemic. However, H1N1 did not worsen the disease burden of pneumonia.

**Keywords** Clinical, epidemiology, H1N1 pneumonia, pandemic, pneumonia burden.

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## Introduction

Since April 17, 2009, when the first two cases of pandemic influenza A(H1N1) virus infection were reported in California, transmission of the virus has rapidly spread throughout the world.[1] The first case of the novel H1N1 virus in Cairo, Egypt, was discovered on June 2, 2009, in a 12-year-old girl traveling from the USA with her mother. The second and third cases were discovered on June 7, 2009, in two students at the American University of Cairo. On June 11, 2009, there were 12 total reported cases of H1N1 influenza cases in Egypt[2], and the World Health Organization (WHO) raised the Pandemic Alert Level to Phase 6, indicating that a global pandemic had begun.[3] Although initial reports suggested that illness associated with pandemic 2009 influenza A (H1N1) infection may be mild compared with the illness of the 1918 influenza pandemic, data on the clinical features and populations at risk for complications from pandemic 2009 influenza A (H1N1) infection are still emerging.[4–6]

The pandemic H1N1 (2009–2010) virus has shown patterns of death and illness not normally associated with influenza infections. Most of the deaths caused by the pandemic influenza have occurred within high-risk groups. Many of the severe cases have been attributed to viral pneumonia, which is more difficult to treat than the

bacterial pneumonia usually associated with seasonal influenza. Many of these patients have required intensive care.[7]

Worldwide, the infectivity and disease burden of the new influenza virus pandemic were overestimated because of limited clinical experience concerning patient presentation and outcome of those infected with the novel H1N1 virus. Therefore, this study aimed to compare the epidemiologic and clinical criteria as well as the disease burden among H1N1 RT-PCR-positive and RT-PCR-negative pneumonic patients during the 2009–2010 pandemic in Mansoura University Hospitals, Egypt.

## Subjects and methods

### Locality

The study was carried out in the chest department isolation unit in Mansoura University Hospitals (MUHs), Egypt. This isolation unit consisted of six rooms designed and equipped according to the WHO criteria for isolation of infectious diseases and an ICU unit with mechanical ventilation for cases with respiratory failure.[8]

### Study population

A review was completed of 198 total case reports, prepared according to WHO 2009,[8] for adult patients admitted to the isolation unit in the chest department of MUHs, Egypt during the 2009–2010 H1N1 pandemic from December 17, 2009, through February 14, 2010. Of these patients, 70 had influenza-like illness (ILI), 66 had ILI with risk factors, 19 had severe acute respiratory illness (SARI), and 43 had pneumonia. Throat swabs were acquired from 128 patients immediately following admission and before starting antiviral drugs.[9] The swabs were taken within 3 days from start of suspected symptoms of ILI and repeated in RT-PCR-negative pneumonia patients. These samples include all patients who were diagnosed with ILI with influenza risk factors, SARI, and pneumonia. The total number of H1N1 cases confirmed by RT-PCR was 27. Of these patients, 20 had pneumonia, three had SARI, and four had ILI with influenza risk factors. The overall number of deaths reported was seven, of which three cases had H1N1-confirmed pneumonia, one had H1N1-confirmed SARI, and three had H1N1-negative pneumonia (Figure 1).

All admitted cases of pneumonia diagnosed during the study period were sorted into either H1N1 RT-PCR-positive or H1N1 RT-PCR-negative groups. The diagnosis of pneumonia was made chiefly on the basis of clinical findings by physical examination and plain chest x-ray. H1N1 was confirmed using an RT-PCR detection technique.[10]

### Study design

A hospital record-based, case–control study was conducted for all adult pneumonic patients admitted to the isolation unit in the chest department during the study period. The case group included 20 pneumonic patients with H1N1 confirmed by RT-PCR, and the control group consisted of 23 H1N1 RT-PCR-negative cases. Formal ethics institutional review board approval was obtained, and informed consent from the patients/next of kin was not required.

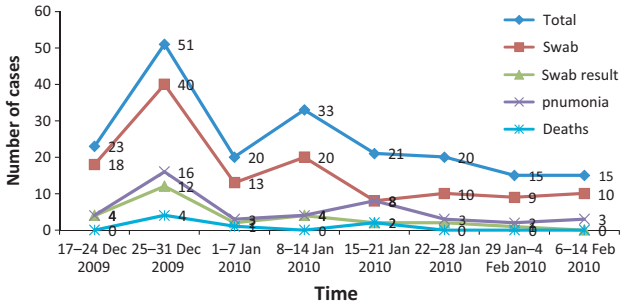


**Figure 1.** Total – total number of admissions: 198 (70 ILI, 66 ILI with risk factors, 19 with SARI and 43 with pneumonia). Swab – total number of swabs collected: 128 (for cases with ILI with risk factors, SARI and pneumonia). Swab Result – total number of confirmed H1N1 cases by RT-PCR: 27 (20 with pneumonia, 3 with SARI and 4 with ILI plus risk factors). Pneumonia – total number of pneumonia cases: 43 (20 PCR-positive and 23 PCR-negative). Deaths – total number of deaths: 7 (3 confirmed with pneumonia, 1 confirmed with SARI, 3 negative for pneumonia).

### Study tools

All recruited patients were subjected to the following procedures:

**1.** A specially designed questionnaire concerning the patient's demographic data including age, sex, residence, marital status, smoking habits, and occupation was administered. Also, information concerning the presence of WHO-recommended H1N1 risk factors (as determined by the WHO)[8] and clinical data relevant to the chest and other body systems were collected.

**2.** Throat cultures were collected using sterile plastic-shafted swabs with a Dacron tip. The swabs were placed into collection vials containing 1–3 ml of viral transport medium. All specimens were kept at 4°C for <72 hours before the test.

**3.** Three duplex reverse transcriptase-PCR assays were run on each specimen to detect matrix gene targets specific for influenza A and influenza B as well as hemagglutinin gene targets specific for influenza A subtypes H1 seasonal, H1 pandemic, and H3.

**4.** RT-PCR assays to detect H1N1 were completed in central laboratories of the Egyptian Ministry of Health and supervised by WHO Regional Office for the Eastern Mediterranean laboratories in Cairo, Egypt.

**5.** Laboratory assessments including complete blood count (CBC), HIV testing, blood gases, blood glucose, and renal and liver function tests were performed.

**6.** Plain chest x-ray.


 

### Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 11 (SPSS Inc., Chicago, IL, USA). H1N1-positive and H1N1-negative groups were compared regarding demographic criteria, risk factors for H1N1, and clinical and radiological data using the chi-square test for qualitative variables and student's *t*-test for quantitative variables. The odds ratio and 95% confidence interval were calculated for each risk factor. $P \leq 0{\cdot}05$ was considered statistically significant.

## Results

A review of the total suspected and confirmed cases of H1N1 treated in the chest department isolation units in MUHs during the 2009–2010 pandemic revealed one main peak during the last week of December 2009 (Figure 1).

Table 1 summarizes the demographic data of the studied patients. In H1N1 pneumonic cases, the patient age ranged from 19 to 71 years (mean: 37·90 ± 16·31), and most of the patients (55%) belonged to the 25- to 49-year age group. However, in H1N1-negative pneumonic cases, patient age ranged from 18 to 79 years (mean: 48·04 ± 18·06) and most patients belonged to the 50-to 64-year age group. No statistically significant differences were found between H1N1-positive and H1N1-negative groups for the other demographic criteria collected.

There were no significant differences between the studied groups for the reviewed laboratory and radiological data including CBC, blood gases, and liver and kidney function tests. HIV testing was negative for all studied cases.

Importantly and as shown in Table 2, no statistically significant difference was observed between both groups of patients regarding the duration lasting from start of symptoms to swab taken ($P > 0{\cdot}05$). The frequency of sore throat, dyspnea, and gastrointestinal (GIT) symptoms (vomiting and diarrhea) was significantly higher in H1N1 cases ($P = 0{\cdot}005$, 0·002, 0·02 respectively) than in H1N1-negative cases. All studied pneumonic patients presented with fever on the day of admission.

**Table 1.** Sociodemographic criteria of pneumonic patients with and without H1N1 during the 2009–2010 pandemic

| Sociodemographic criteria | H1N1 RT-PCR positive | H1NI RT-PCR negative | Test of significance | *P*-value |
|---|---|---|---|---|
| Age:mean ± SD | 37·90 ± 16·31 | 48·04 ± 18·06 | $t = 1{\cdot}88$ | 0·06 |
| 18–24 | 4 (20·0%) | 3 (13·0%) | $\chi^2 = 8{\cdot}59$ | 0·03* |
| 25–49 | 11 (55·0%) | 5 (21·7%) | | |
| 50–64 | 2 (10·0%) | 11 (47·8%) | | |
| >65 | 3 (15·0%) | 4 (17·4%) | | |
| Sex | | | | |
| Male | 9 (45·00%) | 9 (39·10%) | 0·151 | 0·763 |
| Female | 11 (55·00%) | 14 (60·90%) | | |
| Smoking | | | | |
| Non-smokers | 15 (75·00%) | 18 (78·30%) | 0·064 | 1·000 |
| Smokers | 5 (25·00%) | 5 (21·70%) | | |
| Residence | | | | |
| Urban | 12 (60·00%) | 9 (39·10%) | 1·86 | 0·227 |
| Rural | 8 (40·00%) | 14 (60·90%) | | |
| Occupation | | | | |
| House wife | 9 (45·00%) | 8 (34·80%) | 5·945 | 0·653 |
| Skilled worker | 1 (5·00%) | 3 (13·00%) | | |
| Farmer | 2 (10·00%) | 3 (13·00%) | | |
| Governmental employer | 0 (0·00%) | 3 (13·00%) | | |
| Retired | 1 (5·00%) | 1 (4·30%) | | |
| Sales/trade worker | 2 (10·00%) | 1 (4·30%) | | |
| Healthcare workers | 1 (5·00%) | 2 (8·70%) | | |
| Student | 3 (15·00%) | 2 (8·70%) | | |
| Non-skilled | 1 (5·00%) | 0 (0·00%) | | |
| Marital status | | | | |
| Single | 3 (15·00%) | 2 (8·70%) | 1·254 | 0·74 |
| Married | 16 (80·00%) | 19 (82·60%) | | |
| Divorced | 1 (5·00%) | 1 (4·30%) | | |
| Widowed | 0 (0·00%) | 1 (4·30%) | | |

*Statistically significant ($P < 0{\cdot}05$).

**Table 2.** Clinical criteria for suspicion of H1N1-pneumonia during the 2009–2010 pandemic

| | H1N1 RT-PCR positive | H1NI RT-PCR negative | Test of significance | *P*-value |
|---|---|---|---|---|
| Duration from symptoms to swab taken (mean ± SD days) | 2·25 ± 0·56 | 2·45 ± 0·75 | T = 0·98 | 0·33 |
| Sore throat | 16 (80·00%) | 8 (34·40%) | $\chi^2$ = 8·869 | 0·005* |
| Dry cough | 18 (90·00%) | 17 (73·90%) | 1·828 | 0·250 |
| Dyspnea | 16 (80·00%) | 7 (30·40%) | 10·564 | 0·002* |
| Chest pain | 2 (10·00%) | 4 (17·40%) | 0·669 | 0·403 |
| Gastrointestinal (vomiting and diarrhea) | 4 (20·00%) | 0 (0·00%) | 5·07 | 0·02* |

*Statistically significant ($P < 0·05$).

**Table 3.** Risk factors for H1N1 RT-PCR-positive pneumonia

| Risk factors | H1N1 RT-PCR positive (%) | H1N1 RT-PCR negative (%) | OR* (95% confidence interval) | *P*-value |
|---|---|---|---|---|
| History of contact with confirmed H1N1 case | 3 (15·0) | 0 (0·00) | – | 0·09 |
| Chronic respiratory diseases (BA = 2, COPD = 2, IPF = 1) | 5 (25·00) | 5 (21·7) | 1·20 (0·29–4·94) | 0·81 |
| Cardiovascular disease (rheumatic heart disease) | 5 (25·00) | 0 (0·00) | – | 0·01** |
| Pregnancy | 6 (30·0) | 1 (4·30) | 9·43 (1·02– 86·86) | 002** |
| Diabetes mellitus | 4 (20·00) | 4 (17·4) | 0·84 (0·18–3·91) | 0·81 |
| Leukemia (AML) | 3 (15·00) | 0 (0·00) | – | 0·09 |
| Morbid obesity (BMI >40) | 1 (5·00) | 3 (13·0) | 0·35 (0·03–3·67) | 0·61 |
| Renal failure | 1 (5·00) | 4 (17·4) | 0·25 (0·02–2·44) | 0·35 |
| Liver cell failure | 1 (5·00) | 6 (26·1) | 0·14 (0·01–1·36) | 0·10 |
| Healthcare workers | 2 (5·00) | 1 (4·30) | 2·44 (0·20 –29·76) | 0·46 |
| Presence of at least one risk factor | 16 (80·00) | 15 (65·20) | 2·13 (0·53–8·57) | 0·32 |
| Presence of at least two risk factors | 9 (45·00) | 7 (30·10) | 1·87 (0·53–6·53) | 0·36 |

*OR (odds ratio).
**Statistically significant ($P < 0·05$).

Table 3 demonstrates 80% of confirmed H1N1 pneumonia cases also had at least one risk factor, the most frequent of which were pregnancy (six cases), chronic respiratory disease (five cases), rheumatic heart disease (five cases), diabetes mellitus (four cases), and leukemia (three cases). On the other hand, liver cell failure, chronic respiratory disease, and renal failure were the most frequent among H1N1 negative pneumonia cases. However, univariate analysis of these factors revealed that pregnancy and rheumatic heart disease were the only significant risk factors for H1N1 in pneumonic patients (OR = 9·43, $P = 0·02$ and $P = 0·01$, respectively). Presence of at least one or two risk factors were higher in H1N1 cases compared to H1N1-negative cases with statistical insignificant difference ($P > 0·05$).

Complications such as GIT complaints (vomiting and diarrhea) (four cases), hemoptysis (three cases), and pleural effusion (one case) were reported only in H1N1 pneumonic patients with statistical significant difference compared to H1N1-negative cases ($P = 0·01$).

Lastly, as shown in Table 4, there was no significant increase in H1N1 disease burden among pneumonic patients ($P > 0·05$).

## Discussion

Influenza is an important cause of morbidity and mortality.[1] A WHO report, published on February 5, 2010,[11] emphasized that pandemic influenza transmission in Egypt peaked in late December 2009 and early January 2010, with a substantial decline in the number of new cases in January 2010. This is consistent with the disease pattern observed in the present study, where one main peak of transmission was found during the last week of December 2009 with substantial decreases until the end of study.

Pneumonia is recognized as the most important complication of influenza.[12] Lower respiratory infection in patients with influenza may be caused directly by viral invasion[13] or result from secondary bacterial complications.[14]


 

**Table 4.** Disease burden (hospital stay, ICU admission and mortality) in pneumonic patients with and without H1N1 RT-PCR-positive pneumonia during the 2009–2010 pandemic

| | H1N1 RT-PCR positive | H1NI RT-PCR negative | Test of significance | *P*-value |
|---|---|---|---|---|
| Hospital stay | 5·80 ± 2·64 | 5·30 ± 3·11 | 0·558 | 0·580 |
| ICU admission | 5 (25·00%) | 5 (21·70%) | 0·064 | 0·8 |
| Deaths | 3 (15·00%) | 3 (13·00%) | 0·034 | 0·81 |

In the present study, 43 community-acquired pneumonia (CAP) cases were admitted during the 2009/2010 H1N1 pandemic in chest department isolation units of MUHs. Of these patients, H1N1 was confirmed in 20 cases. Accordingly, nearly half of the CAP cases diagnosed during the H1N1 influenza pandemic were caused by H1N1 infection. Gomez-Gomez *et al.* reported that 18 of 50 pneumonia cases were H1N1-positive during the 2009 pandemic.[15]

The rate of H1N1 infection in the USA was highest among individuals <24 years of age with relative sparing of adults over the age of 60.[16,17] Similar patterns of infection were observed in England.[18] In this study, H1N1-positive pneumonia significantly affected young adults (25–49 years), while more than half of H1N1-negative pneumonic patients were over the age of 50. This is similar to Mexico, where more than half of pneumonia patients were between 13 and 47 years of age.[19] Why these severe manifestations of influenza infections occurred in young adults during this outbreak remains unknown.[15]

According to Jain *et al.* (2009),[20] approximately 70% of confirmed H1N1 cases have had at least one underlying risk factor for influenza complication. In studying these factors in pneumonic patients, this percentage increase slightly to about 80%, but 65% of the patient had underlying medical condition and three patients (15%) had risk of contact to suspected or confirmed cases. Furthermore, 45% of the H1N1-positive pneumonia patients had two underlying medical conditions, which increase the risk of complications in influenza patients. In the USA, more than 70% of H1N1 hospitalized patients and approximately 80% of fatal cases have had underlying conditions considered to pose a high risk for complications associated with seasonal influenza including pregnancy, which is the most important of these factors.[9] Also, these findings are consistent with those of Gomez *et al.*[15] in San Luis Potosi, Mexico, who reported that two-thirds of patients hospitalized with pneumonia had underlying health disorders.

The WHO [21] has been closely monitoring the clinical severity of this pandemic since its onset. The clinical spectrum of the pandemic H1N1 2009 virus is broad from mild upper respiratory tract illness to severe complication such as pneumonia, which can result in death. In the present study, sore throat, dyspnea, and gastrointestinal symptoms in the form of vomiting and diarrhea were significantly more frequent in H1N1-confirmed pneumonic cases. Therefore, the presence of these clinical signs could increase the suspicion of H1N1 in pneumonic cases acquired during a pandemic. This is in accordance with the findings of the Novel Swine Origin Influenza A (H1N1) Virus Investigation team,[22] which reported that vomiting and diarrhea were more frequent in H1N1 influenza patients than in those with seasonal influenza. GIT (vomiting and diarrhea), hemoptysis, and pleural effusion were more frequently reported in H1N1-positive pneumonic patients than in H1N1-negative patients, but these complications did not result in increased ICU admission or deaths.

The occurrence of progressive disease with bilateral pulmonary consolidation or acute respiratory distress syndrome and associated with high death rates has been described for patients with influenza-associated pneumonia, particularly those with infections caused by new subtypes of the influenza virus.[23,24] Also, the burden and character of the disease in low-resource settings are still incompletely understood.[25] In our locality, which is considered to be a low-resource country, there were no significant increases in disease burden when considering hospital stay, ICU admission, and mortality in H1N1-confirmed CAP when compared to non-H1N1 CAP (Table 4). This unexpected lack of difference in the disease burden could be related to early diagnosis and early start of antiviral treatment in combination with antibiotics. Treatment regimens of third-generation cephalosporin plus macrolides or quinolone according to the patient's condition were started immediately after the throat swab was taken, i.e. within 24–48 hours from the start of ILI symptoms before the throat culture results were even available. This treatment regimen is recommended by Lee *et al.* and Blumentals *et al.*,[26,27] who emphasized that early diagnosis and prompt antiviral treatment seem to be the best measures for avoiding serious illness caused by the H1N1 influenza virus. Perez-Padilla *et al.*[28] reported that contributing factors for increased H1N1 complications and deaths include delayed admission and delayed initiation of oseltamivir. Also, Louie, Jain *et al.*[20,29] reported that early therapy with oseltamivir in patients with the 2009 H1N1 virus infection may reduce the duration of hospitalization and the risk of progression to severe disease requiring ICU admission or resulting in death.

There are several limitations to our study. First, the relative small number of participants. Second, only pneumonia patients were included. Third, other causes of acute pneumonia (such as other viruses and bacterial infection) were not excluded. In addition, the study included only adult patient and lost patients below the age of 18 years old.

In conclusion, H1N1 pneumonia was observed more frequently in young adults. Sore throat, dyspnea, and presence of GIT complaints increased the suspicion of H1N1 positivity in pneumonia during the H1N1 pandemic. However, H1N1 did not worsen the disease burden of pneumonia.

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