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## **Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain**

*Critical Care* 2009, **13**:R148 doi:10.1186/cc8044

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**ISSN** 1364-8535

**Article type** Research

**Submission date** 7 August 2009

**Acceptance date** 11 September 2009

**Publication date** 11 September 2009

**Article URL** <http://ccforum.com/content/13/5/R148>

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## Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain

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## ABSTRACT

**Introduction:** Patients with influenza A (H1N1)v infection have developed rapidly progressive lower respiratory tract disease resulting in respiratory failure. We describe the clinical and epidemiologic characteristics of the first 32 persons reported to be admitted to the intensive care unit (ICU) due to influenza A (H1N1)v infection in Spain.

**Methods:** We used medical chart reviews to collect data on ICU adult patients reported in a standardized form. Influenza A (H1N1)v infection was confirmed in specimens using real-time reverse transcriptase-polymerase-chain-reaction (RT PCR) assay.

**Results:** Illness onset of the 32 patients occurred between June 23 and July 31, 2009. The median age was 36 years (IQR = 31 - 52). Ten (31.2%) were obese, 2 (6.3%) pregnant and 16 (50%) had pre-existing medical complications. Twenty-nine (90.6%) had primary viral pneumonitis, 2 (6.3%) exacerbation of structural respiratory disease and 1 (3.1%) secondary bacterial pneumonia. Twenty-four patients (75.0%) developed multiorgan dysfunction, 7 (21.9%) received renal replacement techniques and 24 (75.0%) required mechanical ventilation. Six patients died within 28 days, with two additional late deaths. Oseltamivir administration delay ranged from 2 to 8 days after illness onset, 31.2% received high-dose (300mg/day), and treatment duration ranged from 5 to 10 days (mean  $8.0 \pm 3.3$ ).

**Conclusions:** Over a 5-week period, influenza A (H1N1)v infection led to ICU admission in 32 adult patients, with frequently observed severe hypoxemia and a relatively high case-fatality rate. Clinicians should be aware of pulmonary complications of influenza A (H1N1)v infection, particularly in pregnant and young obese but previously healthy persons.

## INTRODUCTION

On August 21, a total of 177 countries reported 182,166 cases on influenza A (H1N1)v infection, 1799 of which were fatal [1]. Perez-Padilla et al. [2] reported 18 persons with laboratory-confirmed novel influenza A (H1N1) hospitalized at National Institute of Respiratory Diseases (INER) in Mexico . A Centers for Disease Control and Prevention (CDC) report in May provided details of the 30 patients who were hospitalized in California, of whom six required admission to ICU and 4 required mechanical ventilation [3]. In New York City, 909 patients with confirmed pandemic H1N1 influenza have been reported as of July 8; 225 (25%) have required ICU care and 124 (14%) have required mechanical ventilation with 59 attributed deaths [4].

As August 25, 93 deaths linked to the pandemic have been reported in Europe, with 16 deaths in Spain and 59 in UK [5]. Patients admitted to the ICU are voluntarily reported to a registry of the Spanish Society of Critical Care Medicine (SEMICYUC). This report summarizes the clinical characteristics of a series of the first 32 patients reported to this ICU register, with special interest in those developing severe respiratory failure.

## MATERIALS AND METHODS

Data abstracted for this study were obtained from a voluntary registry instituted by the Spanish Society of Critical Care Medicine (SEMICYUC) after the first known ICU case. Inclusion criteria consisted in: a) Febrile (>38 C) acute illness; b) Respiratory symptoms consistent with cough, sore throat, myalgia or influenza-like illness; c) Acute respiratory failure requiring ICU admission; plus microbiologic confirmation of novel influenza A (H1N1)v. Data were reported by the attending physician reviewing medical charts, radiologic and laboratory records. The consecutive initial reports notified until august 1, 2009 were eligible for this study. Children under 15 years old were not enrolled in this registry.

This study was approved by the ethical board of Joan XXIII University Hospital, Tarragona ( Spain). Patient identification remained anonymous and informed consent was waived due to the observational nature of the study and that this activity is an emergency public health response. All tests and procedures were ordered by the attending physicians.

Nasopharyngeal-swab specimens were collected at admission and respiratory secretions were also obtained in intubated patients. RT-PCR testing was done in accordance with published guidelines from the Centers for Disease Control (CDC) [6]. H1N1 testing was performed in each institution or centralized in a reference laboratory when not available. A “confirmed case” was defined as an acute respiratory illness with laboratory-confirmed pandemic H1N1 virus infection by real-time reverse-transcriptase PCR or viral culture [7]. Only “confirmed cases” were included in the current study.

Definition of community-acquired pneumonia was based on current ATS/IDSA guidelines [8].

Primary viral pneumonia was defined in patients presenting during the acute phase of influenza virus illness with acute respiratory distress and unequivocal alveolar opacification involving two or more lobes with respiratory and blood bacterial cultures negative. Secondary bacterial pneumonia was considered in patients with confirmation of influenza virus infection that shows recurrence of

fever, increase in cough and production of purulent sputum plus positive bacterial respiratory or blood cultures [9] Bronchoalveolar lavage (BAL) was not systematically performed by the high risk of generating aerosols. Respiratory cultures were based on tracheal aspirates obtained immediately after intubation. Acute renal failure was defined as need for renal replacement therapy following the International Consensus Conference [10].

The ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation, and type of antibiotic and antiviral therapy administered, were not standardized and were made by the attending physician.

The following information was recorded: demographic data, comorbidities, time of illness onset and hospital admission, time to first dose of antiviral delivery, microbiological finding, and chest radiological findings at ICU admission. Intubation and mechanical ventilation requirements, adverse events during ICU stay (e.g. need for vasopressor drugs, or renal replacement techniques) and laboratory finding at ICU admission were also recorded. To determine the severity of illness, the APACHE II score [11] was determined in all patients within 24 hours of ICU admission. In addition, organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system [12]

#### Statistical analysis

Data analysis was conducted using SPSS 13.0 software (Chicago, Illinois). Discrete variables are expressed as counts (percentage) and continuous variables as means  $\pm$  SD or medians with 25<sup>th</sup>-75<sup>th</sup> interquartile (IQR) range. . For the demographic and clinical characteristics of the patients, differences between groups were assessed using the chi-square test and Fisher's exact test for categorical variables and the Student's *t*-test or Mann-Whitney U-test for continuous variables. Survival analysis was performed by Kaplan-Meier survival distribution. P value  $\leq$  0.05 was considered statistically significant.

## RESULTS

On July 31, 2009 a total of 735 cases of influenza A (H1N1)v were confirmed in Spain. Signs at physician presentation are reported in Table 1. Twelve children (25%) and 36 (75%) older than 14 years required critical care [13] (Figure 1). Data from 32 adults in 20 hospitals were reported to be admitted in ICU with severe respiratory failure and are the focus of this report. All patients were confirmed by real-time PCR for pandemic H1N1 virus. Initial PCR for H1N1 virus at ICU admission was negative in 4 patients (12.5%). These patients were later confirmed through further determination in tracheal secretions. The baseline characteristics of patients are shown in Table 2. The median age was 36 years (IQR= 31 to 52). Sixty (50%) patients were between 18 and 40 years of age, and 22 (68.7%) were less than 52 years of age. Only one patient (3.1%) was older than 65. Twenty-one (73.3%) patients were male. Ten (31.2%) patients were reportedly obese (BMI >30) and 2 (6.3%) were pregnant. Asthma (5/32) and exacerbated COPD (4/32) were the main comorbidities reported (Table 3).

Twenty-nine (90.6%) patients had viral pneumonitis, two patients had exacerbated chronic obstructive pulmonary disease (COPD) and one patient with co-infection with by *S. pneumoniae* was reported (documented by respiratory sample culture). All patients received initial empiric antibiotic therapy. Most frequent regimens were beta-lactam plus fluoroquinolones (n=20, 62.5%); Beta-lactam plus macrolides (n=6; 18.7) and beta-lactam plus linezolid (n=5 , 15.6%). One patient (3.1%) received levofloxacin as monotherapy. In addition, 11(34.4%) patients received intravenous steroids at ICU admission. Secondary superinfections by *Pseudomonas aeruginosa* were documented in 3 patients (9.3%) and one presented invasive candidiasis. Mean delay between the onset of symptoms and hospital admission was  $3.7 \pm 2.2$  days (IQR = 2 – 5) and between hospital and ICU admission was  $1.5 \pm 0.8$  days (IQR= 1 – 2).

The mean APACHE II score was  $13.8 \pm 6.4$  and the mean SOFA score was  $7.1 \pm 3.3$ .

Twenty-four patients (75%) developed multiple organ dysfunction syndrome. Twenty patients (62.5%) required vasopressor drugs, and 7 (21.9%) patients received renal replacement techniques due to acute renal failure.

Twenty-four patients (75.0%) required mechanical ventilation (MV), and 8 (33%) of them required prone position. Extracorporeal membrane oxygenation (ECMO) was not implemented. The characteristics of patients according to ventilatory support required are shown in Table 4. Eight (33.3%) patients received non-invasive MV (NIMV) at ICU admission. Six of these patients (75%) required further orotracheal intubation and invasive MV and 2 (33%) died. The SOFA score at admission in patients with NIMV failure ( $8.1 \pm 2.3$ ) was significantly higher ( $p=0.01$ ) than in patients with NIMV successful ( $2.5 \pm 0.7$ ). (Table 4) In survivors, the length of mechanical ventilation ranged from 1 to 50 days (median 10, IQR= 1- 21) . On August 27, 2009, 5 patients still remained on mechanical ventilation and 8 died due to viral pneumonia (Figure 2). Median age of deceased patients was 35 years after a median of 9.5 days of VM (IQR= 3.2 – 15.7).

Chest radiograph findings were abnormal in all patients. Patients with viral primary pneumonia had bilateral patchy alveolar opacities (predominantly basal), affecting three or four quadrants in 23 (71.8%) patients (Figures 3 A). Chest CT scan was performed in only 3 patients (9.4%) and showed airspace consolidation and ground-glass opacity in a multilobar and bilateral distribution (Figure 3B) .Evidence of pulmonary embolism was confirmed in one patient. At the time of ICU admission, 30 (93.7%) patients had elevated lactate dehydrogenase levels (mean  $1521.5 \pm 2471.9$  U/L), 17 (53.1%) above 1000 IU per liter. Twenty-three (71.8%) patients had elevated aminotransferases levels (AST =  $203.5 \pm 498.4$  U/L and ALT=  $156.1 \pm 336.2$  U/L) and twenty-six (81.2%) patients had increased (mean  $2100 \pm 34311$  U/L) creatinine kinase levels (range 226 to 3047 U/L). C-reactive protein (CRP) was assessed in 12 patients (37.5%) with a mean of  $33.8 \pm 25.1$  mg/dL and Procalcitonin (PCT) in 8 (25%) with a mean of  $1.5 \pm 2.1$  ng/ml. Nine patients (28.1%) had leucopenia  $< 3000/\text{mm}^3$  (mean

7038.4  $\pm$  5847.9 leukocytes/ mm<sup>3</sup>), only 4 (12.5%) patients had more than 10.000 leukocytes / mm<sup>3</sup> and 4 (12.5%) patients had thrombocytopenia <100.000/mm<sup>3</sup> (mean 175.000  $\pm$  68.000 /mm<sup>3</sup>).

Eleven (32.3%) patients had elevated creatinine levels( >1.3 mg/dL) at hospital admission.

In all hospitals, infection control measures were put in place, such as isolation of infected patients, use of personal protective equipment (PPE) for health care workers, and strict hand hygiene.

However, only two infected health care workers were reported.

The estimated median number of days from illness onset to initiation of antiviral treatment was 4 days (range 2-8 days). Twenty-one patients (65.6%) received antiviral empiric treatment before testing results were available. All patients were administered oseltamivir, including higher-dose oseltamivir (up to 150 mg orally twice a day) in 10 (31.2%) patients with dose adjustment for decreased renal function. The duration (mean  $\pm$  SD) of treatment with oseltamivir was 8.0 $\pm$ 3.3 (IQR= 5 -10) days.

## DISCUSSION

This report provides details of the first 32 documented patients with influenza A (H1N1)v infection hospitalized in ICU in Spain. Overall, one out of 20 confirmed cases of Influenza A (H1N1)v in Spain required critical care. Most of them had refractory hypoxemia and required advanced mechanical ventilation and at least one third of intubated patients died. This patient group represents the most severely ill subset of persons with influenza A (H1N1)v infection and it is notable for the predominance of males and the high prevalence of obesity.

The pulmonary compromise in this report suggests that severe pulmonary damage occurred as a result of primary viral pneumonia. Although data are not available, this damage also might be attributable to secondary host immune responses (eg. through cytokine dysregulation triggered by high viral replication).

Only 9 of the patients in this series had underlying conditions associated with a higher risk for seasonal influenza complications. Obesity has a higher prevalence of comorbid conditions.

However, our series confirms that obesity, even in absence of other comorbidities, is a frequent association with viral primary pneumonia in young healthy people. Conditions associated with an increased risk for complications from seasonal influenza include extremes of age, pregnancy, chronic underlying medical conditions and being a resident in nursing homes [4,7]. However, fatal disease associated with influenza A (H1N1)v infection has occurred among previously healthy young people [2].

Further analysis of cases by severe Influenza A (H1N1)v infection worldwide is needed. ICU patients in Mexico [2] mainly presented with viral primary pneumonia and mortality was extremely higher. Preliminary information from Australia [13] and USA [3,4] documented other presentations also common (acute exacerbation in COPD patients or bacterial co-infection) which are associated with better outcomes. Computed tomography of the lungs confirmed pulmonary emboli very often at

admission or as a cause of further deterioration in the USA [3], being uncommon in Australia and in our European series. A former report [14] of two patients with rapidly progressive hypoxemia associated with influenza A (H3N2) virus infection noted that they received a initial diagnosis of acute pulmonary embolism.

A common report, is prolonged time to negativize virus excretion [15] associated with need for higher oseltamivir dosing and longer duration of treatment than standard therapy (75 mg orally twice a day). Indeed, limited data for seasonal influenza suggest that doubling the oseltamivir dose is well tolerated with a comparable adverse event profile. Moreover, some reports [4,16] suggested that doubling the dose may be more effective for H5N1 (avian influenza) patients with severe pulmonary disease. Until additional data are available, higher oseltamivir dosage (eg 150 mg orally twice a day for adults) and extending the duration of therapy should be considered for critically ill patients with influenza A (H1N1)v infection.

Clinicians caring for patients with suspected influenza A (H1N1)v infection should monitor them for rapid respiratory clinical deterioration, especially to increased oxygenation requirements. Empiric antiviral treatment is recommended for all hospitalized patients at admission with suspected influenza A virus infection, including all persons who have received a diagnosis of community-acquired pneumonia, even before diagnostic testing results are available. In hospitalized persons with seasonal or avian influenza A (H5N1), a reduction of mortality has been reported even when oseltamivir treatment was initiated later than 48h after illness onset [15-18]. Clinicians should be aware of the false negative results [3] of rapid influenza diagnostic tests (particularly enzyme immunoassay tests). At least 10% of patients with positive real-time PCR tests in respiratory secretions at intubation have reported prior false negative tests in nasopharyngeal swabs. Finally, empiric antibiotic agents also should be used for suspected bacterial co-infection.

## CONCLUSIONS

Primary viral pneumonia is the main cause of ICU admission in (H1N1)v infected patients, developing severe respiratory failure, which is associated with a relatively high case-fatality. An international registry of patients with influenza A (H1N1)v infection requiring ICU admission is needed. Clinicians should be aware of pulmonary complications of influenza A (H1N1)v infection, particularly in pregnant and young obese but previously healthy persons.

### Key messages

- Patients with pneumonia and high clinical suspicion for influenza A (H1N1)v infection should receive continuous oxygen monitoring and addition of oseltamivir treatment should be not delayed.
- Negative result of RT-PCR at admission should not exclude influenza A (H1N1)v diagnosis due to the presence of false negative in 10% of nasopharyngeal-swab specimens.
- Most patients are admitted to the ICU by primary viral pneumonia after mean of 1.5 days of hospital admission.
- An international registry of ICU patients with Influenza A (H1N1)v infection is warranted.

### Abbreviations

APACHE II: Acute Physiology And Chronic Health Evaluation II; ARDS: Acute Respiratory Distress Syndrome; ATS: American Thoracic Society; BMI: Body mass index; CAP: Community-acquired pneumonia; CDC: Centers for Disease Control and Prevention; CRP: C-reactive protein; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive Care Unit; IDSA: Infectious Disease Society of

America; MV: Mechanical Ventilation; NIVM: Non-invasive Mechanical ventilation; PCT:

Procalcitonin; RT-PCR: Real-time Polymerase Chain Reaction; SOFA: Sequential Organ Failure

Assessment scoring system.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

AR has substantial contribution to development database, design, analysis, interpretation of data, and writes the final manuscript.

EGM has an important contribution to acquisition and analysis of data

IP; SL; CJ; MA; GJ; RSS; ME; DNSF; MS; FM; AM; GR, AP, SR, VL;OP and GB have an important contribution to acquisition and analysis of data

ALF and MP have been involved in revising it critically for important intellectual content.

JR and CL have substantial contribution to conception, design, analysis, interpretation of data, and the final manuscript version. They approved the final version to be published.

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## **ACKNOWLEDGEMENTS**

This study has been supported in part by SEMICYUC (Sociedad Española de Medicina Intensiva, Criticos y Unidades Coronarias) , Generalitat de Catalunya Grant (AGAUR/SGR 09/1226), CIBERes Enfermedades Respiratorias (06/06/036) and Institut Recerca Pere Virgili (IISPV).

Written consent for photograph clinical publication (x-ray chest and CT scan) was obtained from the patient.

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Table 1. Percentage of signs and symptom of Influenza A (H1N1)v in confirmed cases

Fever (96%)
Cough (88%)
Myalgia (69%)
Headache (59%)
Sore throat (58%)
Sudden onset of symptoms (46%)
Malaise (30%)

Source: Ministerio de Salud y Política Social [13].

Table 2: Characteristics of 32 patients who had confirmed H1N1 viral primary pneumonitis

<b>Variables</b>	<b>Value</b>
<b>Age, yr</b> Mean (SD) Median (IQR)	40 (13.9) 36 (31-52)
<b>Male sex</b> , n (%)	21 (73.3)
<b>APACHE II score</b> , mean (SD)	13.8 (6.4)
<b>SOFA score</b> , mean (SD)	7.1 (3.3)
<b>Days from onset symptoms to ICU admission</b> Mean (SD) Median (IQR)	3.9 (2.2) 3 (2- 6)
<b>Days from ICU admission to diagnosis</b> Mean (SD) Median (IQR)	3.3 (3.1) 2 (1- 6)
<b>Days from onset symptoms to first antiviral dose</b> Mean (SD) Median (IQR)	5.7 (5.1) 4 (1 – 8)
<b>Laboratory finding</b> , median (IQR) Leukocyte count (per mm <sup>3</sup> ) Platelets count (per mm <sup>3</sup> ) Serum Lactate dehydrogenase (U/L) Serum Creatine Kinase (U/L) Serum creatinine (mg/dL) AST (U/L) ALT (U/L)	5650 (3000 -9200) 152.000 (124.00 – 227.000) 953 (728 – 1230) 392 (226 -3047) 0.87 (0.63 – 1.22) 62 (38 – 119) 51 (35 – 111)
<b>Mechanical ventilation on admission</b> , n (%) NO Non-invasive Invasive	8 (25) 2 (6.2) 22 (68.8)
<b>Adverse event</b> , n (%) Vasopressor drugs Hemodialysis Hemofiltration Refractory hypoxemia requiring prone ventilation Secondary superinfection	20 (62.5) 2 (6.2) 5 (15.6) 8 (25.0) 3 (9.3)
<b>Opacity in initial x-ray chest</b> , n (%) 1/4 quadrants 2/4 quadrants 3/4 quadrants 4/4 quadrants	5 (15.6) 4 (12.5) 8 (25.0) 15 (46.9)

Table 3. Most common risk factors for pandemic H1N1 Influenza in the ICU

Risk Factor	Cases (n=32)
Obesity	10
BMI>40	4
BMI 30-40	6
Asthma	5
COPD	4
Pregnancy	2
Heart Failure	1
Arterial Hypertension	1
Chronic Renal Failure	1
Diabetes mellitus	1
HIV	1
Neuromuscular disease	1
Hematologic disease	1
None	15

BMI= Body mass index; COPD: Chronic Obstructive Pulmonary Disease; HIV= positive human immunodeficiency virus.

Table 4: Characteristics of 32 patients according to ventilator support required

Variable	Non-Ventilated (n=8)	Non-Invasive ventilation		Initially Intubated n= 16
		Successful (n=2)	Failure (n=6)	
APACHE II Score				
Mean (SD)	9.5 (4.9)	9.5 (0.7)	15.3 (5.6)	15.2 (7.6)
IQR 25-75	4 – 16	9 -10	10 – 24	8 -38
SOFA score				
Mean (SD)	4.7 (1.7)	2.5 (0.7)*	8.1 (2.3)**	7.8 (3.5)
IQR 25 – 75	3 – 7	2 – 3	5 – 11	4 – 16
Age , yr				
Mean (SD)	39.2 (14.7)	42.5 (13.4)	44.0 (15.1)	38.7 (14.0)
IQR 25 – 75	17 – 58	33 - 52	10 – 57	16 – 70
Opacity lung quadrants				
Mean (SD)	2.9 (1.2)	2.5 (2.1)	2.8 (0.9)	3.3 (1.1)
LDH , U/L				
Mean (SD)	751 (361)	1140 (374)	918 (408)	2170 (3400)
IQR 25 – 75	195 – 1166	880 – 1400	354 – 1450	440 – 12200
CK, U/L				
Mean (SD)	2480 (4500)	2800 (3200)	4850 (4200)	2300 (3800)
IQR 25 – 75	66 – 9300	500 – 5100	122 - 9400	207 – 10800
28-day Mortality,n(%)***	0	0	2 (33)	4 (25)

\* vs. \*\* p=0.01

\*\*\* Two additional patients died by refractory hypoxemia after 31 and 65 days of mechanical ventilation.

APACHE II score: Acute Physiology And Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment ; IQR: Interquartil 25-75; LDH: Lactate dehydrogenase; CK: Creatine Kinasa.

## Figure Legends

Figures 1: Number of confirmed cases and clinical attack rate in Spain [13].

Figure 2: Cumulative survival of 32 ICU patients with Influenza A (H1N1)v pneumonia (Censored at 28 days).

Figure 3: Radiograph (3A) / CT scan (3B) of the lung in a patient with viral pneumonitis.

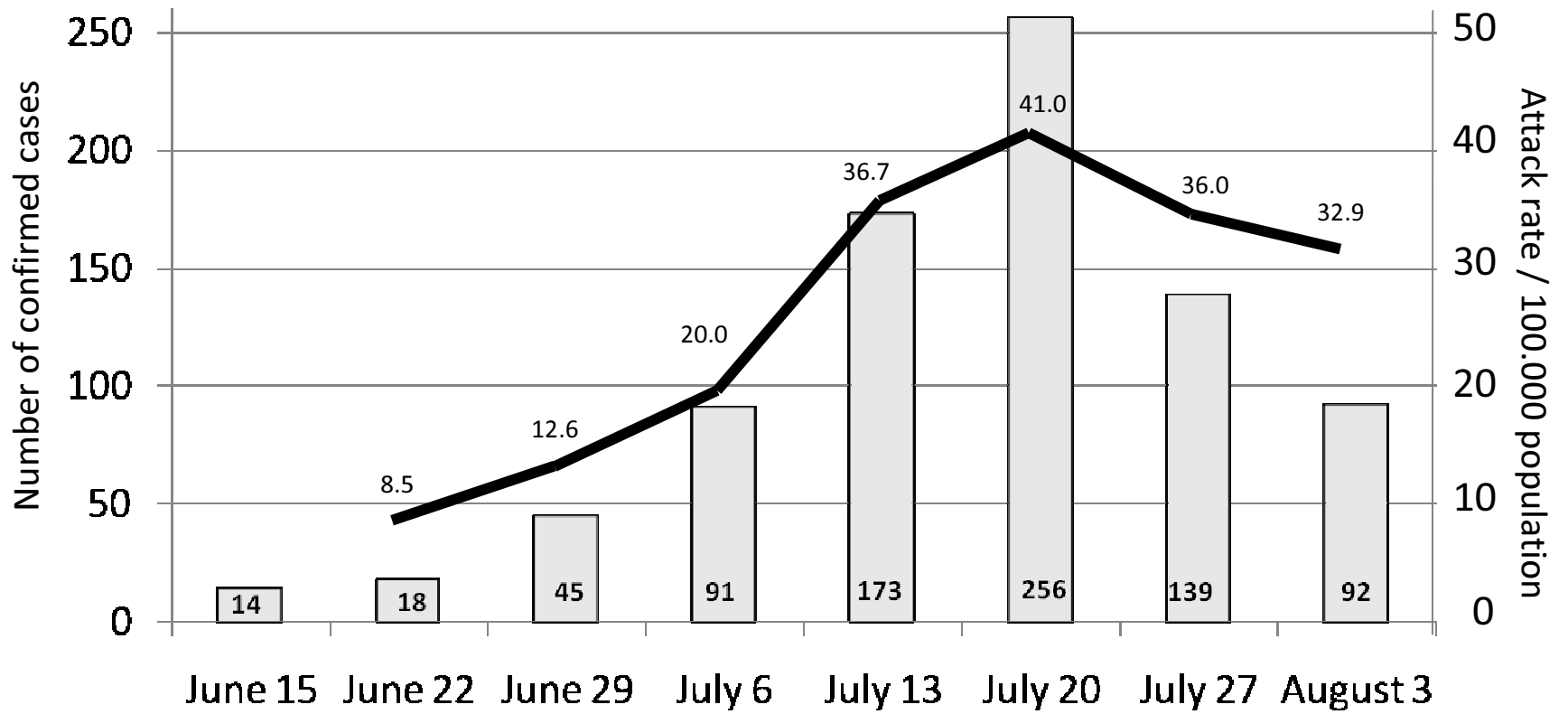


Figure 1

Figure 2:

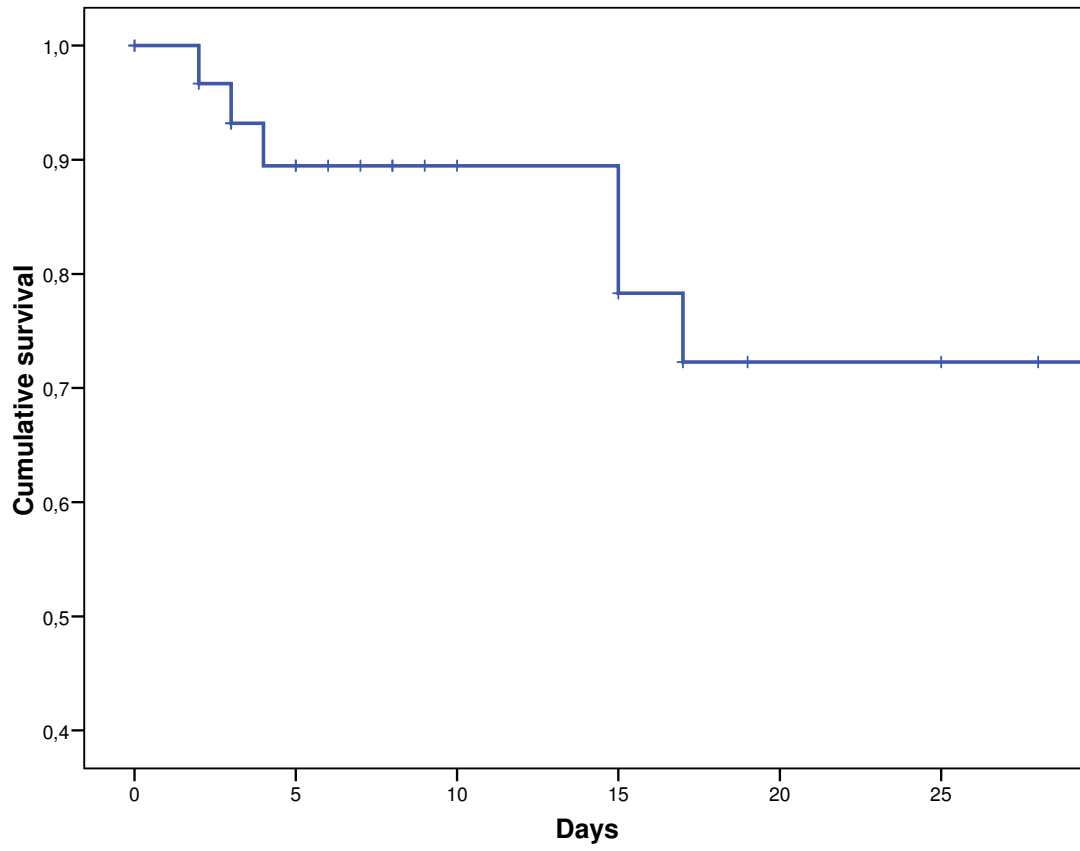


Figure 3A

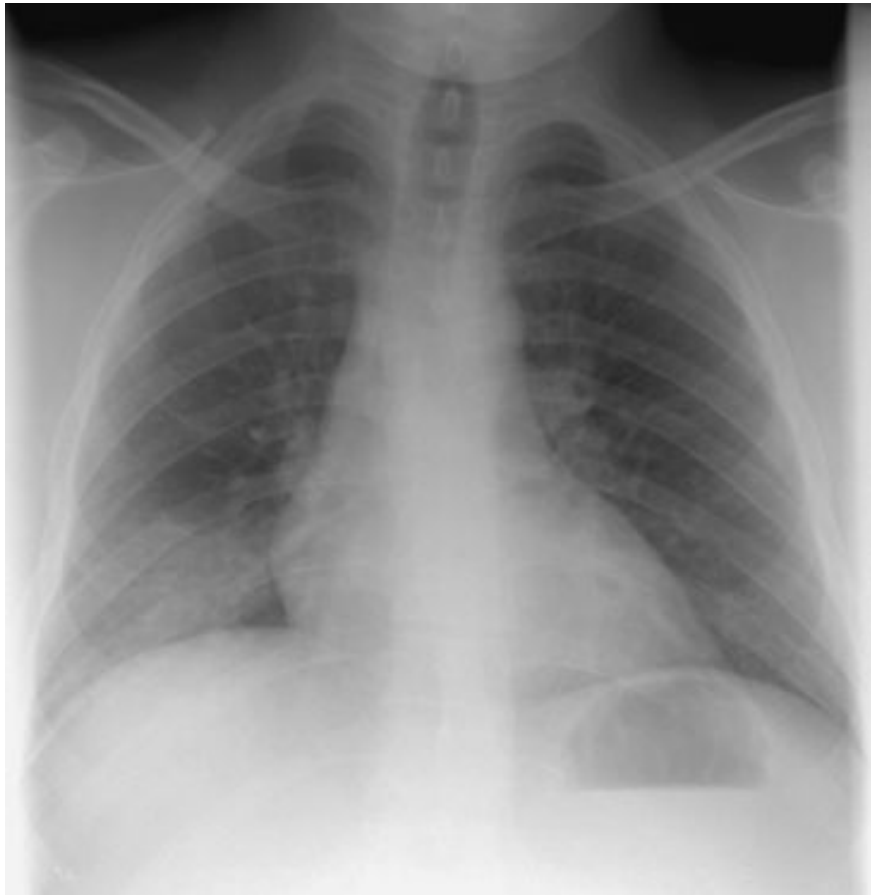


Figure 3B

