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# Characteristics of patients with hospital-acquired influenza A (H1N1)pdm09 virus admitted to the intensive care unit

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## SUMMARY

**Background:** Influenza A (H1N1)pdm09 virus infection acquired in the hospital and in critically ill patients admitted to the intensive care unit (ICU) has been poorly characterized.

*Aim:* To assess the clinical impact of hospital-acquired infection with influenza A (H1N1) pdm09 virus in critically ill patients.

**Methods:** Analysis of a prospective database of the Spanish registry (2009–2015) of patients with severe influenza A admitted to the ICU. Infection was defined as hospital acquired when diagnosis and starting of treatment occurred from the seventh day of hospital stay with no suspicion on hospital admission, and community-acquired when diagnosis was established within the first 48 h of admission.

**Findings:** Of 2421 patients with influenza A (H1N1)pdm09 infection, 224 (9.3%) were classified as hospital-acquired and 1103 (45.6%) as community-acquired (remaining cases unclassified). Intra-ICU mortality was higher in the hospital-acquired group (32.9% vs 18.8%, P < 0.001). Independent factors associated with mortality were hospital-acquired influenza A (H1N1)pdm09 infection (odds ratio: 1.63; 95% confidence interval: 1.37–1.99), APACHE II score on ICU admission (1.09; 1.06–1.11), underlying haematological disease

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<sup>†</sup> See Supplementary Appendix A (online).

(3.19; 1.78-5.73), and need of extrarenal depuration techniques (4.20; 2.61-6.77) and mechanical ventilation (4.34; 2.62-7.21).

**Conclusion:** Influenza A (H1N1)pdm09 infection acquired in the hospital is an independent factor for death in critically ill patients admitted to the ICU.

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## Introduction

Outbreaks of influenza virus infection in hospitalized patients have been reported for many years in groups such as onco-haematological patients, transplant recipients, paediatric patients, and in neonatal intensive care units. <sup>1–5</sup> Since the 2009 pandemic with novel influenza A (H1N1)pdm09 virus, tests for early and rapid diagnosis of viral infections have become widely used. <sup>6</sup> With the wide availability of accurate tests for influenza A (H1N1)pdm09 infection, several outbreaks caused by this virus in units treating immunocompromised patients have been documented. <sup>7–9</sup> In the intensive care units (ICUs), patients with influenza A (H1N1)pdm09 virus infection continue to be a seasonal problem, and experience a high mortality rate. <sup>10,11</sup> However, to our knowledge, no large outbreaks of infection due to influenza A (H1N1)pdm09 virus acquired on ICUs have been published.

In Spain, there is a registry of patients with influenza A virus infection who required ICU admission for their treatment. <sup>12</sup> Most patients with influenza A (H1N1)pdm09 virus infections had community-acquired infections and were admitted early in the course of their illnesses with severe acute respiratory failure requiring respiratory support. A smaller group of patients had nosocomial infection influenza A (H1N1)pdm09 virus. Previous studies have assessed independent factors related with mortality in hospitalized patients infected with the influenza A (H1N1)pdm09 virus, including specifically ICU patients and other specific patient groups. <sup>13–21</sup> However, in none of these has hospital-acquired influenza A (H1N1)pdm09 virus infection been considered as a risk factor for death.

This study was designed to analyse available data from the Spanish Working Group on Severe Pandemic Influenza A (GET-GAG) of the Spanish Society of Critical Care Medicine and Coronary Units (SEMICYUC) (GETGAG/SEMICYUC) registry of patients admitted to the ICU diagnosed with influenza A (H1N1) pdm09 virus infection, in order to assess the clinical profiles and outcomes of those with hospital-acquired infection. It was hypothesized that acquisition of influenza A (H1N1)pdm09 infection in the hospital was an independent risk factor for mortality.

#### Methods

# Design and study population

This was a cohort, observational, and multicentre study based on a secondary analysis of patients included in the GETGAG/SEMICYUC registry. Between January 1<sup>st</sup>, 2009 and December 31<sup>st</sup>, 2015, data for all patients with microbiologically confirmed diagnosis of influenza A (H1N1)pdm09 virus infection admitted to 148 ICUs throughout Spain were included

in the GETGAG/SEMICYUC registry. The identities of patients were anonymized and individual patient informed consent was not obtained given the non-interventional and retrospective nature of the study. The GETGAG/SEMICYUC registry was approved by the Institutional Review Board of Hospital Joan XXIII University Hospital of Tarragona, Spain, and analysis of the present study was approved by the Clinical Research Ethical Committee of Parc de Salut Mar of Barcelona, Spain.

# Case definition

All patients with respiratory infection in which influenza A (H1N1)pdm09 virus was identified by real-time polymerase chain reaction performed according to recommendations of the Centers for Disease Control and Prevention were included in the analysis. <sup>22</sup> Other virological studies were not performed. Clinical manifestations included two or more of the following signs and symptoms: fever (>38°C), cough, bronchial expectoration, and myalgias associated with clinical signs of organ or system failure, such as respiratory failure, haemodynamic instability or altered consciousness. Information was provided by physicians of the participating ICUs according to the patient's medical history, laboratory data, and radiological findings. Patients aged <15 years were not included in the registry.

Patients were classified according to the time at which the diagnosis of influenza A (H1N1)pdm09 virus infection was established. Community acquisition was defined as diagnosis within two days of admission to hospital; cases diagnosed seven or more days after admission, and where there was no suspicion of viral respiratory infection on admission, were defined as hospital-acquired; patients who did not fall into either of the above groups were deemed to be unclassified.

# Data collection

A case report form (CRF) was designed for data collection, including demographics (age, sex); time-related variables (date of hospital admission, date of ICU admission, length of hospital stay and date of diagnosis of influenza A (H1N1)pdm09 virus infection, length of hospital and ICU stay); comorbidities; severity of illness on admission; presenting manifestations of infection; treatments administered (oseltamivir, inotropic drugs, corticoids, mechanical ventilation); and intra-ICU mortality. The severity of infection was assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE II) score within the first 24 h of ICU admission, and the level of organ failure using the Sequential Organ Failure Assessment (SOFA) score on ICU admission. 23,24 Definitions of communityacquired or hospital-acquired pneumonia were those recommended by the American Thoracic Society and the Infectious Diseases Society of America. 25,26

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