Prognosis of hospitalized patients with 2009 H1N1 influenza in Spain: influence of neuraminidase inhibitors

Miguel Delgado-Rodríguez1,2*, Jesús Castilla2,3, Pere Godoy2,4, Vicente Martín2,5, Nuria Soldevila2, Jordi Alonso2,6, Jenaro Astray7, Maretha Baricot2, Rafael Cantón2,8, Ady Castro2, Fernando González-Candelas2,10, José María Mayoral11, José María Quintana2,12, Tomás Pumarola13, Sonia Tamames14, Marc Sáez15 and Angela Domínguez2,16 on behalf of the CIBERESP Cases and Controls in Pandemic Influenza Working Group†

1Universidad de Jaén, Campus de las Lagunillas, 23071 Jaén, Spain; 2CIBERESP, Instituto de Salud Carlos III, Sinesio Delgado 6, 28071 Madrid, Spain; 3Instituto de Salud Pública de Navarra, Leyre 15, 31003 Pamplona, Spain; 4Departament de Salut, Generalitat de Catalunya, Travessera de les Corts 131, 08028 Barcelona, Spain; 5Instituto de Biomedicina, Universidad de León, Campus Universitario de Vegazana, 24071 León, Spain; 6Institut Municipal de Investigación Médica, Barcelona, Dr. Aiguader 80, 08003 Barcelona, Spain; 7Área de Epidemiología, Comunidad de Madrid, Antonio Grello 10, 28029 Madrid, Spain; 8Hospital Universitario Ramón y Cajal, Carretera de Colmenar Viejo km 9.1, 28034 Madrid, Spain; 9CIBER Enfermedades Respiratorias, Recinto Hospital Joan March, Carretera Soller km 12, 07110 Bunyola, Mallorca, Illes Balears, Spain; 10Centro Superior de Investigación en Salud Pública, Universitat de València, Av. de Cataluña 21, 46020 Valencia, Spain; 11Servicio de Vigilancia de Andalucía (Consejería de Salud), Avenida de la Innovación (Edificio Arenas), 41020 Sevilla, Spain; 12Unidad de Investigación, Hospital Galdakao-Usansolo, Barria Labeaga, Galdakao, 48960 Bizkaia, Spain; 13Red Española de Investigación en Patología Infecciosa (REIPI), ISCIII, Sinesio Delgado 6, 28071 Madrid, Spain; 14Dirección General de Salud Pública e Investigación, Junta de Comunidades de Madrid, 28071 Madrid, Spain; 15Universitat de Girona, Emili Grahit 77, 17071 Girona, Spain; 16Universitat de Barcelona, Casanova 143, 4 planta, 08036 Barcelona, Spain

*Corresponding author. Division of Preventive Medicine & Public Health, University of Jaén, Campus de las Lagunillas, 23071-Jaén, Spain.
Tel: +34-953-212-703; Fax: +34-953-212-632; E-mail: mdelgado@ujaen.es
†Other members of the CIBERESP Cases and Controls in Pandemic Influenza Working Group are listed in the Acknowledgements section.

Received 14 December 2011; returned 7 January 2012; revised 28 February 2012; accepted 1 March 2012

Background: The H1N1 influenza pandemic strain has been associated with a poor prognosis in hospitalized patients. The present report evaluates the factors influencing prognosis.

Methods: A total of 813 patients hospitalized with H1N1 influenza in 36 hospitals (nationwide) in Spain were analysed. Detailed histories of variables preceding hospital admission were obtained by interview, validating data on medications and vaccine with their attending physicians. Data on treatment and complications during hospital stay were recorded. As definition of poor outcome, the endpoints of death and admission to intensive care were combined; and as a further outcome, length of stay was used.

Results: The mean age was 38.5 years (SD 22.8 years). There were 10 deaths and 79 admissions to intensive care (combined, 88). The use of neuraminidase inhibitors was reported by 495 patients (60.9%). The variables significantly associated with a poor outcome were diabetes (OR = 2.21, 95% CI = 1.21–4.02), corticosteroid therapy (OR = 3.37, 95% CI = 1.39–8.20) and use of histamine-2 receptor antagonists (OR = 2.68, 95% CI = 1.14–6.36), while the use of neuraminidase inhibitors (OR = 0.57, 95% CI = 0.34–0.94) was protective. Neuraminidase inhibitors within the first 2 days after the influenza onset reduced hospital stay by a mean of 1.9 days (95% CI = 4.7–6.6).

Conclusions: The use of neuraminidase inhibitors decreases the length of hospital stay and admission to intensive care and/or death.

Keywords: prevention, adverse outcomes, length of stay, flu, pandemic

Introduction

Influenza A pandemic H1N1 2009 virus infections began to spread in Spain during spring 2009. Reports suggested high mortality in children and adults associated with the new virus in Mexico1,2 and Argentina,3 as well as in previously healthy young people. Analysis of cases hospitalized in the USA showed a mortality rate of 7%, with 25% of patients being
admitted to the intensive care unit (ICU). A study of 32 patients infected with the pandemic virus strain admitted to Spanish ICUs found a mortality rate of 25%, somewhat lower than in Latin American countries. These findings suggest that the H1N1 virus is more virulent than previous strains.

As there was no specific targeted vaccine giving protection against the H1N1 influenza virus available at the beginning of the outbreak, health authorities began to recommend administration of neuraminidase inhibitors to reduce transmission and/or complications. Various studies have suggested that these drugs are also effective in reducing the severity of the infection.

We reviewed nationwide Spanish data on hospitalized patients with 2009 H1N1 influenza A in order to: (i) evaluate the frequency of adverse outcomes during hospitalization; and (ii) identify the factors influencing poor/good outcome, including the use of neuraminidase inhibitors shortly after the onset of symptoms.

Methods
Study design
We carried out a multicentre study in 36 hospitals from seven Spanish regions (Andalusia, Catalonia, Castile and Leon, Madrid, Navarre, the Basque Country and Valencia). Between July 2009 and February 2010 we selected hospitalized patients with influenza syndrome, acute respiratory infection, septic shock or multiple organ failure in whom influenza virus A (H1N1) 2009 infection was confirmed by real-time reverse transcription PCR (RT-PCR) from nasopharyngeal swabs; haemagglutinin (HA) sequencing was performed. We excluded patients who had nosocomial infection, defined as pandemic virus infection in a patient that appeared ≥48 h after admission for another cause. All information collected was treated as confidential, in strict observance of legislation for observational studies. The study was approved by the Ethics Committees of the hospitals involved, following the Declaration of Helsinki principles. Written informed consent was obtained from all patients included in the study.

Selection of patients
During the pandemic flu all patients suspected of having the disease, either in outpatient clinics or hospitals, were diagnosed by RT-PCR of samples from nasopharyngeal swabs. Within the next 48 h, hospitalized patients were interviewed at the centre. Of these, 23 rejected participation and 12 were excluded because flu had been acquired after hospital admission.

Data collection
The following demographic variables and pre-existing medical conditions were recorded for all study participants: age, sex, ethnicity, educational level, smoking, alcoholism, pregnancy in women aged 15–49 years, history of pneumonia in the previous two years, chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease, renal failure, diabetes, HIV infection, disabling neurological disease, cancer, transplantation, morbid obesity (body mass index ≥40), use of neuraminidase inhibitors before hospital admission (and their timing relative to the onset of symptoms, verified after contacting the prescribing general practitioner), use of other medications in the 90 days before hospital admission (corticosteroids, antibiotics etc.) and treatment received during hospitalization (medications, catheters and mechanical ventilation). For each vaccine, a case was considered vaccinated if the vaccine had been received ≥14 days before the onset of symptoms. Data were collected during hospital admission and the clinical chart was also reviewed after discharge.

The outcome variables were admission to an ICU, in-hospital death and length of hospital stay (in days). Given that the number of deaths was very low, a combined endpoint was classified as ‘poor outcome’: ICU admission and/or in-hospital death.

Statistical analysis
Bivariate comparisons were made using Pearson’s χ² test for categorical variables and Student’s t-test for continuous variables. As a measure of association, the relative risk (OR) and 95% CI were calculated. Logistic regression was applied in the multivariate analysis for dichotomous adverse outcomes. To determine the variables to be included in the multivariate analysis, the procedure described by Sun et al. was followed. Intermediate variables were discarded. We ran two stepwise models, one backward and another forward, including variables with P<0.2. We constructed a list of predictors of mortality identified in other studies. Using information from stepwise models and the list of predictors, a saturated model was built, and by using a heuristic approach, variables that did not change the coefficient of the bundles by more than 10% were discarded, in order to construct a parsimonious model retaining all important confounders.

To analyse the impact of different variables on the length of hospital stay, patients who died were excluded from these analyses. Given that hospital stay did not follow the normal curve, natural logarithms were used. Firstly, to select potential variables related to length of stay, we used Cox regression in the same fashion as described above for the logistic regression analysis. The variables selected by this model were tested by including other potential candidates according to the logistic regression analyses. Secondly, an analysis of covariance was applied to estimate the adjusted means of hospital length of stay. All analyses were made using the Stata 10/SE package (College Station, TX, USA).

Results
There were a total of 813 patients (410 (50.4%) were female, of which 51 (12%) were pregnant). The mean age was 38.5 years (SD 22.8) and 24% were aged <18 years. The use of neuraminidase inhibitors was reported by 495 patients (60.9%), with oseltamivir being administered in all cases but two (zanamivir). During hospitalization, 79 patients (9.7%) were admitted to the ICU and 10 died (1.2%), of whom 9 were not receiving intensive care. No death occurred in pregnant women, of whom only one was admitted to the ICU. The timings of the use of neuraminidase inhibitors before hospital admission were: 332 patients (SD 22.8) and 24% were aged 18 years. The use of neuraminidase inhibitors (OR=2.68, 95% CI=1.14–6.36). Use of neuraminidase inhibitors was protective (OR=0.57, 95% CI=0.34–0.94). Pneumonia at admission, COPD, ex-smoking and liver failure showed a trend to association.
Table 1. Description of the study population (N=813)

| Variable                                      | n (%)       |
|-----------------------------------------------|-------------|
| Sex (female), n (%)                           | 410 (50.4)  |
| pregnant, n (%)                               | 51 (12.4)   |
| Age                                           |             |
| mean (SD)                                     | 38.5 (22.8) |
| median, IQR                                   | 41 (19–55)  |
| ≤18 years, n (%)                              | 195 (24.0)  |
| 19–45, n (%)                                  | 275 (33.8)  |
| 46–65, n (%)                                  | 242 (29.8)  |
| >65, n (%)                                    | 101 (12.4)  |
| Race (Caucasian), n (%)                       | 708 (87.1)  |
| Vaccinated with pandemic H1N1 vaccine, n (%)  | 13 (1.6)    |
| Vaccinated with seasonal influenza vaccine, n | 155 (19.1)  |
| Smoking, n (%)                                |             |
| current                                       | 178 (21.9)  |
| ex-smoker                                     | 128 (15.7)  |
| Alcoholism, n (%)                             | 44 (5.4)    |
| Corticosteroid therapy, n (%)                 | 31 (3.8)    |
| COPD, n (%)                                   | 76 (9.4)    |
| Number of comorbidities, n (%)                |             |
| 0                                             | 242 (29.8)  |
| 1                                             | 195 (24.0)  |
| 2–3                                          | 212 (26.1)  |
| ≥4                                           | 164 (20.2)  |
| Use of neuraminidase inhibitors before admission, n (%) | 495 (60.9) |
| Admission to ICU, n (%)                       | 79 (9.7)    |
| In-hospital death, n (%)                      | 10 (1.2)    |
| Length of hospital stay (days), mean (median, IQR) | 8.5 (5, 3–9) |

The trend analysis for age in the multivariable analysis yielded a P value of 0.11, with advanced age associated with a higher risk of adverse outcome. When the timing of treatment with neuraminidase inhibitors after the onset of influenza was analysed, the benefit was confined to administration within the first 48 h after the onset of symptoms.

Table 3 shows the variables associated with length of hospital stay. The use of neuraminidase inhibitors within the first 2 days after the onset of influenza reduced hospital stay by a mean of 1.9 days (from 6.6 to 4.7, P<0.001), whereas delayed administration was associated with an increase in hospital stay. Pneumonia diagnosed at admission was clearly associated with longer hospital stay, as were comorbidities (COPD, neurological impairment and cardiovascular disease) and some therapies (proton pump inhibitors).

**Discussion**

We found that traditional risk factors associated with hospitalization in patients with influenza (COPD and corticosteroid therapy before admission) were also found in our patients. Likewise, the use of neuraminidase inhibitors reduced the probability of adverse outcomes during hospitalization and significantly shortened the length of stay.

This study is observational and can be affected by several limitations. Kumar11 has recently highlighted the drawbacks of observational studies in estimating the benefits of early viral treatment in the prognosis of flu. We agree that selection bias is difficult to avoid. Immortal time bias or survival-duration-related selection bias imply that the late use of antivirals may be related to a better prognosis, whereas in fact our results suggest the opposite.

Our results show no benefit of late neuraminidase treatment. In Israel, a retrospective cohort study documented a higher rate of complications after admission.12 Severe complications (excluding hypoxia and uncomplicated pneumonia) occurred more frequently with late oseltamivir. In the same way, a Spanish study of ICU patients showed that ICU length of stay, days of mechanical ventilation and mortality were reduced in patients receiving early treatment versus late treatment with oseltamivir.13 These reports do not give comparisons with flu patients without antiviral treatment.

The mortality rate in our study (1.2%) was low in comparison with other studies. This may be due to the fact that our patients were not all admitted to the ICU,14,15 and did not all have pneumonia at hospital admission.15 Even so, the mortality rate was clearly lower than that found in the USA at the beginning of the pandemic (7%)16 or the 4.9% reported in Canada.16 Likewise, the rate of ICU admission (9.7%) was lower than that found in the USA (25%)16 and Canada (16%),16 although it was similar to the 8% reported in New Zealand Maoris.17 Some form of selection bias cannot be completely ruled out as our study patients had to be interviewed to collect data on the use of medications before admission and other risk factors related to disease severity. In a study carried out in Catalonia (north-east Spain), of 773 cases hospitalized, 37.9% were admitted to the ICU.18 In contrast, in Andalusia (southern Spain), 28 out of 311 hospitalized cases (9%) were admitted to an ICU.19 In another Spanish study of patients admitted to the ICU, the mortality rate was 22%.20 Taken together, these data suggest that patients who died shortly after admission were not picked up by our study.

The predisposing factors for a higher probability of adverse outcome during hospitalization were broadly similar to those found in other studies.16,21 In one international series of patients with community-acquired pneumonia, male sex and obesity were predictors of mortality, although we did not find similar results.12

We found a significant association between reductions in ICU admission/death and the administration of neuraminidase inhibitors within the first 48 h after the onset of symptoms, similarly to the findings of Jain et al.4 and other studies.6,7 In these reports none of the pregnant women who died had taken neuraminidase inhibitors within the first two days after the onset of illness.

Early use of neuraminidase inhibitors was associated with shorter hospital stay. Other reports have found no relationship between antiviral treatment and hospital stay.12 In summary, we found that early treatment with neuraminidase inhibitors had a beneficial effect on outcomes during
| Variable                                      | Total | n (%) | OR (95% CI)       | OR^a (95% CI)       |
|----------------------------------------------|-------|-------|-------------------|---------------------|
| **Sex**                                      |       |       |                   |                     |
| female                                       | 410   | 40 (9.8) | 0.80 (0.50–1.28) | 0.87 (0.54–1.40)    |
| male                                         | 403   | 48 (11.9) | 1 (ref.)         | 1 (ref.)            |
| **Age (years)**                              |       |       |                   |                     |
| ≤18                                          | 195   | 13 (6.7)  | 1 (ref.)        | 1 (ref.)           |
| 19–45                                        | 275   | 27 (9.8)  | 1.52 (0.73–3.31) | 1.33 (0.63–2.80)  |
| 46–65                                        | 242   | 33 (13.6) | 2.21 (1.09–4.71) | 1.56 (0.73–3.33)  |
| ≥66                                          | 101   | 15 (14.9) | 2.44 (1.03–5.83) | 1.86 (0.76–4.55)  |
| **Ethnicity**                                |       |       |                   |                     |
| Caucasian                                    | 708   | 82 (11.6) | 0.46 (0.16–1.09) | 0.56 (0.23–1.34)  |
| other                                        | 105   | 6 (5.7)  | 1 (ref.)         | 1 (ref.)           |
| **Use of neuraminidase inhibitors**          |       |       |                   |                     |
| yes                                          | 495   | 49 (9.9)  | 0.79 (0.49–1.26) | 0.57 (0.34–0.94)  |
| ≤48 h within onset of symptoms               | 429   | 36 (8.4)  | 0.66 (0.39–1.09) | 0.46 (0.27–0.80)  |
| >48 h                                        | 66    | 13 (19.7) | 1.75 (0.80–3.63) | 1.29 (0.61–2.70)  |
| no                                           | 318   | 39 (12.3) | 1 (ref.)        | 1 (ref.)           |
| **Vaccinated with pandemic H1N1 vaccine**    |       |       |                   |                     |
| yes                                          | 13    | 2 (15.4)   | 1.51 (0.16–7.08) | 1.65 (0.33–8.23)  |
| no                                           | 800   | 86 (10.8) | 1 (ref.)         | 1 (ref.)           |
| **Vaccinated with seasonal influenza vaccine**|       |       |                   |                     |
| yes                                          | 155   | 15 (9.7)   | 0.86 (0.44–1.57) | 0.60 (0.31–1.15)  |
| no                                           | 658   | 73 (11.1) | 1 (ref.)        | 1 (ref.)           |
| **Smoking**                                  |       |       |                   |                     |
| ex-smoker                                    | 128   | 21 (16.4) | 1.97 (1.07–3.52) | 1.72 (0.94–3.13)  |
| current                                      | 178   | 21 (11.8) | 1.34 (0.74–2.37) | 1.22 (0.68–2.18)  |
| never                                        | 507   | 46 (9.1)   | 1 (ref.)        | 1 (ref.)           |
| **Alcoholism**                               |       |       |                   |                     |
| yes                                          | 44    | 8 (18.2)   | 1.91 (0.74–4.37) | 1.46 (0.62–3.45)  |
| no                                           | 769   | 80 (10.4) | 1 (ref.)        | 1 (ref.)           |
| **COPD**                                     |       |       |                   |                     |
| yes                                          | 76    | 14 (18.4) | 2.02 (1.00–3.87) | 1.76 (0.86–3.57)  |
| no                                           | 663   | 74 (10.0) | 1 (ref.)        | 1 (ref.)           |
| **Cardiovascular disease**                   |       |       |                   |                     |
| yes                                          | 70    | 13 (18.6) | 2.03 (0.97–3.97) | 1.56 (0.76–3.16)  |
| no                                           | 7438  | 75 (10.1) | 1 (ref.)        | 1 (ref.)           |
| **Diabetes**                                 |       |       |                   |                     |
| yes                                          | 98    | 19 (19.4) | 2.25 (1.21–4.02) | 2.21 (1.21–4.02)  |
| no                                           | 715   | 69 (9.7)   | 1 (ref.)        | 1 (ref.)           |
| **Liver failure**                            |       |       |                   |                     |
| yes                                          | 27    | 8 (22.9)   | 2.59 (0.98–6.09) | 2.23 (0.93–5.34)  |
| no                                           | 778   | 80 (10.3) | 1 (ref.)        | 1 (ref.)           |
| **Corticosteroid therapy**                   |       |       |                   |                     |
| yes                                          | 31    | 8 (25.8)   | 3.05 (1.14–7.35) | 3.37 (1.39–8.20)  |
| no                                           | 782   | 80 (10.2) | 1 (ref.)        | 1 (ref.)           |
| **Treatment with histamine-2 receptor antagonists** |       |       |                   |                     |
| yes                                          | 33    | 8 (24.2)   | 2.08 (1.05–6.66) | 2.68 (1.14–6.36)  |
| no                                           | 780   | 80 (10.3) | 1 (ref.)        | 1 (ref.)           |
### Table 2. Continued

| Variable                                | Total | n (%) | OR (95% CI)   | OR\(^a\) (95% CI) |
|-----------------------------------------|-------|-------|---------------|-------------------|
| Pneumonia at admission                  |       |       |               |                   |
| yes                                     | 178   | 26 (12.8) | 1.29 (0.76–2.14) | 1.69 (0.98–2.93) |
| no                                      | 609   | 62 (10.2) | 1 (ref.)      | 1 (ref.)          |
| No. of comorbidities                    |       |       |               |                   |
| 0                                       | 242   | 15 (6.2) | 1 (ref.)      | 1\(^b\) (ref.)   |
| 1                                       | 195   | 19 (9.7) | 1.63 (0.76–3.56) | 1.79 (0.88–3.65) |
| 2–3                                     | 212   | 27 (12.7) | 2.21 (1.09–4.60) | 2.57 (1.31–5.03) |
| ≥4                                      | 164   | 27 (16.5) | 2.98 (1.47–6.24) | 3.86 (1.91–7.79) |

\(^a\)Adjusted by age, sex, antiviral treatment before admission, pneumonia at admission, liver failure, diabetes, cardiovascular disease, treatment with histamine-2 receptor antagonists, corticosteroids, smoking and alcoholism.

\(^b\)Adjusted by age, sex, antiviral treatment before admission and pneumonia at admission.

### Table 3. Length of hospital stay (LOS) in days and association with study variables

| Variable                               | Crude LOS |               | Adjusted LOS |               |
|----------------------------------------|-----------|---------------|--------------|---------------|
|                                       | mean (95% CI) | P | mean (95% CI) | P |
| Use of neuraminidase inhibitors        |           |               |              |               |
| yes                                    |           |               |              |               |
| ≤48 h within onset of symptoms         | 4.9 (4.5–5.3) | 0.001 | 4.7 (4.0–5.4) | <0.001 |
| >48 h                                  | 9.4 (7.6–11.6) | 0.001 | 8.8 (7.7–9.9) | 0.014 |
| no                                     | 6.3 (5.7–7.0) |       | 6.6 (6.0–7.3) |       |
| COPD                                   |           |               |              |               |
| yes                                    | 7.6 (6.2–9.2) | 0.003 | 7.4 (5.9–9.1) | 0.012 |
| no                                     | 5.5 (5.2–5.9) |       | 5.5 (5.2–5.9) |       |
| Antibiotics before admission           |           |               |              |               |
| yes                                    | 6.1 (5.4–6.9) | 0.196 | 6.2 (5.5–7.0) | 0.073 |
| no                                     | 5.5 (5.2–6.0) |       | 5.5 (5.1–5.9) |       |
| Corticosteroids before admission       |           |               |              |               |
| yes                                    | 5.6 (4.9–6.4) | 0.861 | 5.8 (5.4–6.2) | 0.056 |
| no                                     | 5.7 (5.3–6.1) |       | 5.1 (4.5–5.9) |       |
| Proton pump inhibitors                 |           |               |              |               |
| yes                                    | 7.4 (6.3–8.6) | 0.001 | 6.6 (5.6–7.8) | 0.032 |
| no                                     | 5.4 (5.1–5.8) |       | 5.5 (5.1–5.9) |       |
| Pneumonia at admission                 |           |               |              |               |
| yes                                    | 6.1 (5.4–6.9) | 0.148 | 6.7 (5.9–7.6) | 0.004 |
| no                                     | 5.5 (5.2–5.9) |       | 5.4 (5.0–5.8) |       |
| Neurological impairment                |           |               |              |               |
| yes                                    | 7.8 (5.8–10.6) | 0.034 | 8.5 (6.3–11.5) | 0.006 |
| no                                     | 5.6 (5.3–6.0) |       | 5.6 (5.2–5.9) |       |
| Ex-smoker                              |           |               |              |               |
| yes                                    | 6.8 (5.8–7.8) | 0.016 | 6.4 (5.5–7.4) | 0.118 |
| no                                     | 5.5 (5.1–5.9) |       | 5.6 (5.2–5.9) |       |
| Cardiovascular disease                 |           |               |              |               |
| yes                                    | 8.5 (7.0–10.4) | 0.001 | 7.6 (6.2–9.3) | 0.005 |
| no                                     | 5.5 (5.1–5.8) |       | 5.5 (5.2–5.9) |       |
hospitalization and on the length of hospital stay in patients with H1N1 virus infection.

Acknowledgements

Other members of the CIBERESP Cases and Controls in Pandemic Influenza Working Group

Andalusia: E. Azor, J. Carrillo, R. Moyano, J. A. Navarro, M. Vázquez, F. Zafra (Sentinel physicians), M. A. Bueno, M. L. Gómez, M. Mariscal, B. Martínez, J. P. Quesada, M. Sillero (Complejo Hospitalario de Jaén), M. Carnero, J. Fernández-Crehuet, J. del Diego Salas (Hospital Virgen de las Nieves), V. Fuentes (Hospital Costa del Sol), V. Gallardo, E. Pérez (Servicio de Epidemiología), R. López (Hospital Infantia Elena de Huelva), J. R. Maldonado (Hospital de Torrecárdenas), A. Morillo (Hospital Virgen del Rocío), J. M. Navarro, M. Pérez (Laboratorio de Referencia de Gripe), S. Oña (Hospital Carlos Haya), M. J. Pérez (Hospital Virgen de Valme), M. C. Ubago (Hospital Virgen de las Nieves), M. Zurzuella (Hospital Puerta del Mar), Valencia Community: J. Blanquer (Hospital Clínico de Valencia), M. Morales (Hospital Doctor Peset). Castile and Leon: D. Carriedo, F. Diez, I. Fernández, S. Fernandez, M. P. Sanz (Complejo Asistencial Universitario de León), J. J. Castrodeza, A. Pérez (Dirección General de Salud Pública e Investigación, Desarrollo e Innovación), R. Ortiz de Lejarazu (Centro Nacional de Gripe de Valladolid), J. Ortiz (Hospital de El Bierzo), A. Pueyo, J. L. Viejo (Complejo Asistencial de Burgos), P. Redondo (Servicio Territorial de Sanidad y Bienestar Social de León), A. Molina (Instituto de Biomedicina, Universidad de León). Catalonia: A. Agusti, A. Torres, A. Trilla, A. Vilella (Hospital Clinic), F. Babé (Hospital Arnau de Vilanova), L. Blanch, G. Navarro (Hospital de Sabadell), X. Bonfill, J. López-Contreras, V. Pornar, M. T. Puig (Hospital de Sant Pau), E. Borrás, A. Martínez, N. Torner (Dirección General de Salud Pública), C. Bravo, F. Moraga (Hospital Vall d'Hebrón), F. Cafaiell (Universitat Pompeu Fabra), J. Caylà, C. Tortajada (Agencia de Salud Pública de Barcelona), I. García, J. Ruiz (Hospital Germans Trias i Pujol), J. J. García (Hospital Sant Joan de Deu), O. Garín (CIBERESP-Universitat Pompeu Fabra), J. Gea, J. P. Horcajada (Hospital del Mar), N. Hayes (Hospital Clinic CRESIB), A. Rosell (Hospital de Bellvitge). Madrid: C. Álvarez, M. Enríquez, F. Pozo (Hospital 12 de Octubre), F. Baquero, J. C. Galán, A. Robustillo, M. Valdeón (Hospital Universitario Ramón y Cajal), E. Córdoba, F. Dominguez, J. García, R. Génova, E. Gil, S. Jiménez, M. A. Lopaz, J. López, F. Martin, M. L. Martínez, M. Ordóñez, E. Rodríguez, S. Sánchez, C. Valdés (Área de Epidemiología de la Comunidad de Madrid), J. R. Paños, M. Romero (Hospital Universitario La Paz). Navarra: A. Martínez, L. Martínez (Instituto de Salud Pública), M. Ruiz, P. Fanlo, F. Gil, V. Martínez-Artola (Complejo Hospitalario de Navarra), M. E. Urrusa, M. Sota, M. T. Vito, J. Gamboa, F. Pérez-Afonso (Sentinel physicians). The Basque Country: U. Aguine, A. Cascalpestaegui, P. P. Espana, S. Garcia, (Hospital Goldakao), J. M. Antóhama, I. Astigarraga, J. I. Pijoan, I. Pocheville, M. Santiago, J. I. Villate (Hospital de Cruces), J. Arrieta, A. Escobar, M. I. Garrote (Hospital Basurto), A. Bilbao, C. Goraiar (Fundación Vasca de Innovación e Investigación Sanitarias), G. Cilla, J. Korta, E. Pérez Trallera, C. Sarasqueta (Hospital Donostia), F. Esteban, C. Salado, J. L. Lobo (Hospital Txagorritxu), J. Alustiza (Hospital Mendaro).

Funding

This work was supported by the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (Ministry of Science and Innovation, National Institute of Health Carlos III), Programme of Research on Influenza A/H1N1 (GR09/0030) and Agency for the Management of Grants for University Research (AGAUR, 2009/SGR 42). The funders had no role in the study design, data collection, analysis, the decision to publish or the preparation of the manuscript.

Transparency declarations

None to declare.

References

1. Chowell G, Bertozi SM, Calchera MA et al. Severe respiratory disease concurrent with the circulation of H1N1 influenza. N Engl J Med 2009; 361: 674–9.
2. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009; 361: 680–9.
3. Libster R, Bugna J, Covelli S et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med 2010; 362: 45–55.
4. Jain S, Kamimoto L, Bramley AM et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med 2009; 361: 1935–44.
5. Rodriguez A, Socas L, Guerrero JE et al. [Pandemic influenza A in the ICU: experience in Spain and Latin America. GETGAG/SEMICYUC/ (Spanish Working Group on Severe Pandemic Influenza A/SEMICYUC)]. Med Intens 2010; 34: 87–94.
6. Jamieson DJ, Honein MA, Rasmussen SA et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009; 374: 451–8.
7. Louie JK, Acosta M, Jamieson DJ et al. California Pandemic (H1N1) Working Group. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 2010; 362: 27–35.
8. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. J Clin Epidemiol 1996; 49: 907–16.
9. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol 1993; 138: 923–36.
10. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989; 129: 125–37.
11. Kumar A. Early versus late oseltamivir treatment in severely ill patients with 2009 pandemic influenza A (H1N1): speed is life. J Antimicrob Chemother 2011; 66: 959–63.
12. Hila V, Chowers M, Levi-Vinograd I et al. Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): retrospective cohort study. J Antimicrob Chemother 2011; 66: 1150–5.
13. Rodriguez A, Diaz E, Martin-Loeches I et al. Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A. J Antimicrob Chemother 2011; 66: 1140–9.
14. ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009; 361: 1925–34.
15. Riquelme R, Jiménez P, Videla AJ et al. Predicting mortality in hospitalized patients with 2009 H1N1 influenza pneumonia. Int J Tuberc Lung Dis 2011; 15: 542–6.
16. Campbell A, Rodin R, Kropp R et al. Risk of severe outcomes among patients admitted to hospital with pandemic (H1N1) influenza. CMAJ 2010; 182: 349–55.
17. Verrall A, Norton K, Rooker S et al. Hospitalizations for Pandemic (H1N1) 2009 among Maori and Pacific Islanders, New Zealand. Emerg Infect Dis 2010; 16: 100–2.
H1N1 influenza and hospitalization

18 Godoy P, Rodés A, Álvarez J et al. [Characteristics of cases hospitalized for severe pandemic (H1N1) 2009 in Catalonia]. Rev Esp Salud Publ 2011; 85: 53 – 9.

19 Mayoral Cortes JM, Puell Gómez L, Pérez Morilla E et al. Behaviour of the pandemic H1N1 influenza virus in Andalusia, Spain, at the onset of the 2009–10 season. Euro Surveill 2009; 14: 1 – 4.

20 Santa-Olalla Peralta P, Cortes García M, Limia Sánchez A et al. [Critically ill patients with 2009 pandemic influenza A (H1N1) infection in Spain: factors associated with death, April 2009-January 2010]. Rev Esp Salud Publ 2010; 84: 547–67.

21 Crum-Cianflone NF, Blair PJ, Faix D et al. Clinical and epidemiologic characteristics of an outbreak of novel H1N1 (Swine Origin) influenza A virus among United States Military beneficiaries. Clin Infect Dis 2009; 49: 1801–10.

22 McGeer A, Green KA, Plevneshi A et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis 2007; 45: 1568–75.