Surveillance of hospitalised patients with influenza-like illness during pandemic influenza A(H1N1) season in Sicily, April 2009 – December 2010

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This paper describes the epidemiology of hospitalised cases with influenza-like illness (ILI) and laboratory-confirmed influenza A cases in Sicily (Italy) during the 2009 influenza pandemic. The first ILI case diagnosed as infected with pandemic influenza A(H1N1)2009 in Sicily was reported in June 2009 and it rapidly became the dominant circulating strain. In the period from 30 April 2009 through 31 December 2010, a total of 2,636 people in Sicily were hospitalised for ILI and 1,193 were laboratory-confirmed for influenza A. Basic demographic and clinical information for all hospitalised patients was collected and population mortality rates (PMRs) and case fatality ratios (CFRs) were calculated. The median age of hospitalised patients infected with pandemic influenza A(H1N1)2009 was significantly lower than that of hospitalised ILI cases in general (18.0 vs. 32.1 years; $p < 0.0001$). Among adults, women were more susceptible than men. The majority of clinical presentations were mild, but 6.6% of hospitalised patients required admission to an intensive care unit, of whom 26.3% had confirmed influenza A. Twenty-four fatal cases were documented. The age group of 45–54 year-olds showed the highest PMRs once hospitalised, while CFRs were higher in elderly patients of 65 years and older. All fatal cases were confirmed as influenza A(H1N1)2009 and most of them had established risk factors for influenza complications.

Introduction

Before the emergence of the influenza A(H1N1)2009 virus in April 2009 [1], descriptions of clinical illness due to human infection with swine-origin influenza had been limited to sporadic cases and an outbreak on a military base in 1976 [2]. During the pandemic period, more than 214 countries and territories worldwide reported laboratory-confirmed cases of influenza A(H1N1)2009, and approximately 2,900 deaths were reported in Europe [3].

In Italy, the virus was first detected on 2 May 2009 in an adult man returning from Mexico [4]. Since then, more than 27,000 confirmed cases have been reported, including 260 deaths [3,5]. In Sicily, the largest island of Italy with a population of about 5 million inhabitants, the first laboratory-confirmed case of influenza A(H1N1)2009 was detected on 7 June 2009 in a young man returning from the United States, and the first fatal case was reported on 19 September 2009 in a woman in her 40s who did not have any underlying diseases or known risk factors.

According to the guidelines of the Italian Government Department of Health, a Regional Pandemic Influenza Preparedness and Response Plan was published in August 2009 in order to enhance the epidemiological/virological surveillance for influenza. A team of general practitioners and paediatricians (members of the national network INFLUNET) were involved as sentinel practitioners, while several hospital wards throughout Sicily exceptionally participated in the surveillance of hospitalised patients with influenza-like illness (ILI) for severe acute respiratory infection (SARI) potentially related to pandemic influenza A(H1N1)2009.

The aim of the present study was to report the influenza surveillance data describing the epidemiological characteristics of patients with ILI symptoms, laboratory-confirmed infections with pandemic influenza A(H1N1)2009, and fatal cases that occurred among hospitalised patients in Sicily from April 2009 through December 2010.

Methods

Surveillance and data collection

We obtained ILI surveillance data and results of laboratory-tested samples for all individuals who sought hospital medical care for ILI symptoms in the period

from 30 April 2009 through 31 December 2010 in Sicily. These data were part of the nationwide active sentinel surveillance network (INFLUNET) that is responsible for seasonal influenza surveillance in Italy and combines clinical and virological information [5].

The molecular epidemiology laboratory located in the hygiene section of the Department of Health Promotion Sciences at the University Hospital (Azienda Ospedaliera Universitaria Policlinico 'P. Giaccone') in Palermo, member of the INFLUNET network, was appointed as the Sicilian reference laboratory for the virological surveillance of 2009 pandemic influenza by decree of the Regional Government Department of Health.

According to the Regional Pandemic Influenza Preparedness and Response Plan [6], about 110 different hospital wards throughout the region (mainly from infectious diseases, paediatrics and neonatology, and internal medicine departments) sent nasopharynx swabs and/or bronchoalveolar lavages (BAL) to the diagnostic reference laboratory together with standardised questionnaires including demographic and epidemiological/clinical information (e.g. comorbid conditions).

All patient data were entered in a database and reported weekly to the National Institute of Health (Istituto Superiore di Sanità; ISS) in Rome. Data collected through INFLUNET were also part of the European Influenza Surveillance Network (EISN) database coordinated by the European Centre for Disease Prevention and Control (ECDC) [5].

Case definitions and laboratory diagnosis

A case of ILI was defined as an individual admitted to hospital with acute respiratory illness and at least one of the following symptoms: acute onset of fever ($\geq 38^{\circ}\text{C}$), sore throat, headache, cough, muscle pain, nasal obstruction, general discomfort or asthenia.

Nasopharyngeal swabs and/or BAL from patients with ILI were homogeneously collected and transported to the regional reference laboratory by using Virocult swabs (MWE, Medical Wire, UK), and tested by real-time RT-PCR according to a recommended protocol from the United States Centers for Disease Control and Prevention (CDC) [7] on an ABI Prism 7000 real-time PCR instrument (Applied Biosystems, US).

Each suspected case of ILI was laboratory-confirmed as negative for influenza A or positive for pandemic influenza A(H1N1)2009, influenza A(H3N2) or unsubtypeable influenza A, as appropriate. Samples negative for pandemic influenza A(H1N1)2009 but positive for influenza A were directly sequenced by cycle sequencing, using BigDye terminator chemistry v3.1 on an ABI Prism 3130xl automatic sequencer (Applied Biosystems, US) following in-house protocols for diagnosis confirmation (protocols available upon request). Diagnosis of

influenza was invariably provided within 8–24 hours after the receipt of the sample.

A fatal case was defined as a resident of Sicily with laboratory-confirmed pandemic influenza A(H1N1)2009, who died after 27 April 2009.

Statistical analysis

Demographic and clinical information was analysed using descriptive analysis. Data were aggregated into 10-year intervals (except for the first group of 0–4 year-olds) according to age at admission. Medians and interquartile ranges (IQRs) were used to describe continuous variables, while frequency analyses for categorical variables were described with percentages.

Comparisons of continuous variables were conducted using Student's *t*-test or the Mann–Whitney U-test, according to data distribution, and a *p* value < 0.05 was considered to indicate statistical significance. Univariate logistic regression was used to examine the relation between variables of interest (age and sex) and severity of disease. For this purpose, patients were categorised into two groups according to their hospital admission in a medical intensive care unit (ICUs) or not, and stratified by age according to three arbitrarily chosen age groups (≤ 4 years, 15–54 years and ≥ 55 years). The age-group 5–14 years was used as a reference group. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Overall and age-specific population mortality rates (PMRs) for pandemic influenza A(H1N1)2009 were cumulatively calculated over the study period using the 2009 population for Sicily reported by the National Institute of Statistics [8], whereas for the comparison of mortality between different countries in Europe, standardised PMRs were estimated based on the EUROSTAT European population data and data provided by the ECDC [3,9]. Moreover, the case fatality ratios (CRFs) were calculated overall and by age group. The numerator was the reported number of fatal cases and the denominator was the cumulative number of hospitalised patients with ILI admission included in the study, both with a laboratory confirmation of influenza A(H1N1)2009 infection.

Statistical analyses were carried out with the use of STATA software for Apple (version 11.1 MP, StataCorp, US).

Results

Surveillance data for influenza-like illness and confirmed cases of influenza A(H1N1)2009

A total of 2,636 cases of ILI ($n=1,204$ females (45.7%) and $n=1,432$ males (54.3%)) were hospitalised during the study period (Table 1). Overall, 1,193 of 2,636 (45.3%) were confirmed as influenza A, and of those, 1,146 (96.1%) were pandemic influenza A(H1N1)2009, 42 (3.5%) were unsubtypeable influenza A strains,

and only five (0.4%) were seasonal influenza A(H3N2) strains.

Among the influenza A-positive samples, females and males accounted for 47.9% and 52.1%, respectively. The median age of hospitalised patients was 25.4 years (IQR: 40.3 years), and a difference was found between influenza A-negative ILI cases and confirmed influenza A(H1N1)2009 cases (32.1 years and 18.0 years, respectively) ($p < 0.0001$). When aggregated by age, ILI patients were similarly represented within each age group, while influenza A-positive individuals were younger (5–14 years) and their proportion progressively decreased in older groups ($p < 0.0001$).

A total of 175 patients (6.6% of those included in the study), 129 (8.9%) with influenza A-negative ILI and 46 (3.8%) with influenza A infection were admitted to ICUs. On average, ICU patients with laboratory-confirmed influenza A(H1N1)2009 infection were younger than ICU patients with influenza A-negative ILI (median age: 40.8 years and 53.7 years, respectively). Moreover, 16 ICU patients (five influenza A-negative

ILI and 11 influenza A(H1N1)2009-positive) developed severe clinical complications and required extra-corporeal membrane oxygenation (ECMO) treatment. A total of 24 ICU patients, all diagnosed as positive for pandemic influenza A(H1N1)2009 infection, died.

Figure 1 depicts the trend of total ILI and laboratory-confirmed influenza A(H1N1)2009 cases reported during the study period, by week of sampling. During the early phase of the 2009 surveillance, the majority of cases were imported from the United States/Canada, the United Kingdom/Ireland, Spain, and Malta, or related to contact with imported confirmed cases. Few cases of ILI and confirmed pandemic influenza A(H1N1)2009 were hospitalised, and only five ILI cases were identified as cases of seasonal influenza A(H3N2) (weeks 24 to 29).

All cases hospitalised from 20 July 2009 (week 30) onwards were cases of pandemic influenza A(H1N1)2009, and starting from 10 August 2009 only autochthonous cases were detected. A slight increase in the number of ILI cases was observed at the end of

TABLE 1

Characteristics of the study population of influenza-like illness cases, Sicily 30 April 2009–31 December 2010 (n=2,636)

	Total ILI cases	Influenza A-negative cases	Influenza A-positive cases
Hospitalised patients [n (% by row)]	2,636	1,443 (54.7)	1,193 (45.3)
InfluenzaA(H1N1)2009			1,146 (96.1)
InfluenzaA unsubtypeable			42 (3.5)
InfluenzaA(H3N2)			5 (0.4)
Sex [n (%)]			
Female	1,204 (45.7)	633 (43.9)	571 (47.9)
Male	1,432 (54.3)	810 (56.1)	622 (52.1)
Age [median IQR]			
All	25.4 (40.3)	32.1 (46.4)	18.0 (30.8)*
Admitted to ICU	50.5 (49.4)	53.7 (53.6)	40.8 (41.0)*
Managed with ECMO	37.1 (13.0)	40.0 (7.0)	35.6 (12.0)*
Deaths	48.5 (18.5)	NA	48.5 (18.5)
Age groups [n (%)]			
0–4 (years)	371 (14.1)	199 (13.8)	172 (14.4) ^a
5–14 (years)	434 (16.5)	168 (11.6)	266 (22.3) ^a
15–24 (years)	348 (13.2)	155 (10.7)	193 (16.2) ^a
25–34 (years)	274 (10.4)	134 (9.3)	140 (11.7) ^a
35–44 (years)	256 (9.7)	133 (9.2)	123 (10.3) ^a
45–54 (years)	231 (8.8)	131 (9.1)	100 (8.4) ^a
55–64 (years)	193 (7.3)	121 (8.4)	72 (6.0) ^a
65–74 (years)	129 (4.9)	106 (7.3)	23 (1.9) ^a
≥75 (years)	137 (5.2)	127 (8.8)	10 (0.8) ^a
Unknown	263 (9.9)	169 (11.7)	94 (7.9)
ICU admission [n (% by row)]	175 (6.6)	129 (8.9)	46 (3.8)
ECMO	16 (9.1)	5 (31.2)	11 (68.8) ^b
Deaths	24 (13.7)	NA	24 (100.0) ^b

ECMO: extra-corporeal membrane oxygenation; ICU: intensive care unit; ILI: influenza-like illness; IQR: interquartile range; NA: not applicable.

* statistically significant at $p < 0.0001$.

^a Trend analysis for proportions: $p < 0.0001$.

^b Laboratory-confirmed cases of influenza A(H1N1)2009.

September (week 39), and the peak was reached in mid-November (week 47), followed by a rapid decrease; only sporadic cases were confirmed from the turn of the year 2009/2010.

The percentage of samples positive for influenza A(H1N1)2009 was calculated for each age group, as well as the females/males ratio for these percentages (Figure 2). The highest values, both of absolute numbers and percentage of influenza A(H1N1)2009-positive samples, were reported in the age group of 5–14 year-olds, with more than 60% of positive samples. While the ratio ranged from 0.8 to 1.1 among younger individuals, it was higher among adults and elderly individuals (range: 1.4–2.1).

In order to evaluate the presence of possible correlates of the severity of disease, influenza A-negative ILI and laboratory-confirmed influenza A(H1N1)2009 cases were divided into two categories: admitted to ICU or not. Table 2 shows the odds ratios of disease severity that were calculated for confirmed cases of influenza A(H1N1)2009, comparing hospitalised non-severe cases with cases admitted to ICU for each of three arbitrarily chosen age groups ≤ 4 years, 15–54 years and ≥ 55 years vs. The reference group of 5–14 year-old patients. Overall, the odds ratio of disease severity was 3.07 (95% CI: 1.06–8.95) among patients 15–54 years of age, 3.95 (95% CI: 1.03–15.08) among elderly patients (≥ 55 years), and 1.61 (95% CI: 0.43–6.09) in the youngest group. In our dataset, sex was not correlated to the severity of disease.

Mortality and case fatality ratios for influenza A(H1N1)2009 in Sicily

Twenty-four laboratory-confirmed fatal cases of influenza A(H1N1)2009 (median age: 48.5 years, range: 13–75 years; 11 males) were reported in Sicily from 19 September 2009 to 31 December 2010. The overall PMR for pandemic influenza was 4.81 per million inhabitants (standardised rate based on the European population: 5.01 per million inhabitants) and appeared to increase progressively with age. It was lower in adolescents (1.89 per million inhabitants) and peaked at 13.2 per million inhabitants in the age group of 45–54 year-olds. No fatal cases were reported in children under five years of age, in the 15–24 year-olds and in elderly 75 years and older (Figure 3).

The overall CFR was 2.0%, among male patients 1.8% and among female patients 2.3%. There was evidence of differences in the age-specific CFRs, with higher values in individuals between 65 and 75 years of age (CFR: 17.4%) compared to those aged 0–64 years (CFR: 1.9%) (Figure 3).

Table 3 reports the individual risk factors for 22 of 24 pandemic influenza A(H1N1) fatal cases in Sicily. Nineteen of these 22 had an underlying risk factor for severe influenza, obesity being the most common ($n=8$), while three individuals did not have any underlying known risk factors or comorbidities. Overall, eight of 19 fatal cases had only one risk factor, whereas 11 fatal cases suffered from more than one underlying condition.

FIGURE 1

Weekly distribution of hospitalised cases of influenza-like illness ($n=2,636$), laboratory-confirmed ($n=1,146$) and fatal ($n=24$) influenza A(H1N1)2009 in Sicily, 30 April 2009–31 December 2010

FIGURE 2

Proportion of samples positive for influenza A(H1N1)2009 and females/male ratio, by age-group, Sicily, 30 April 2009–31 December 2010

TABLE 3

Reported comorbid conditions of fatal influenza A(H1N1)2009 cases, Sicily, 30 April 2009–31 December 2010 (n=22)

Underlying risk factors	Total ^a
Patients with reported risk factors	19
One comorbid condition	8
More than one comorbid condition	11
Most common risk factors	
Obesity	8
Chronic heart disease	7
Chronic neurological disease	6
Chronic respiratory disease	5
Diabetes	5
Patients with no risk factors	3

^a Some patients had more than one underlying disease

TABLE 2

Univariable predictors of disease severity among hospitalised confirmed cases of influenza A(H1N1)2009, Sicily, 30 April 2009–31 December 2010 (n=1,146)

Confirmed influenza A(H1N1) cases	All subjects	Disease severity		
		Non-severe outcome	Admission to ICU	OR (95% CI)
Sex (n=1,146)				
Female	550	527	24	Reference group
Male	596	579	22	0.69 (0.37–1.28)
Age groups (years) (n=1,099)				
≤4	204	198	6	1.61 (0.43–6.09)
5–14	264	259	5	Reference group
15–54	544	518	26	3.07 (1.06–8.95)
≥55	87	82	5	3.95 (1.03–15.08)

CI: confidence interval; ICU: intensive care unit; OR: odds ratio.

FIGURE 3

Population mortality rates and case fatality ratios of influenza A(H1N1)2009 cases, by age group, Sicily, 30 April 2009–31 December 2010 (n=24)

Discussion

This paper summarises the epidemiology of influenza-like illness and pandemic influenza A(H1N1)2009 in hospitalised patients in Sicily, from April 2009 to December 2010. Influenza A(H1N1)2009 cases were significantly younger than ILI cases not confirmed as influenza A infections ($p < 0.0001$), and the proportion of ILI samples positive for influenza A(H1N1)2009 reached a maximum of about 60% in younger people (5–14 years old). Similar numbers have been reported from other European countries [10,11].

In our series, higher percentages of influenza A(H1N1)2009-positive samples were reported among adult women (age groups 45–54, 55–64, 65–75 and >75 years) compared with younger female individuals. Different hypotheses could explain this. Adult women seem to be more prone to the disease than men [10], as supported in part by studies on the increased risk of severe illness in pregnant women [12]. Moreover, other authors have reported that women may be more exposed to airborne infections because of their role in child care or because they may have more contacts with older people who live in the family or with other close relatives [10].

In order to identify predictors of disease severity, the surveillance data were stratified by location of care (ICU admissions and hospital admissions other than ICU) and age group. Several studies have evaluated the risk of a severe outcome in association with specific individual risk factors such as age and sex, as well as pre-existing medical conditions. In Canada, the risk of admission to ICU was greater for females, and patients with milder disease were younger than those admitted to ICU [13]. Similar results were also found in England [14]. In our paper, higher values compared to the reference group (5–14 years of age) were observed amongst adults aged 15–54 years (OR: 3.07; 95% CI: 1.06–8.95) and older (OR: 3.95; 95% CI: 1.03–15.08), while sex was not a predictor of disease severity.

Twenty-four deaths were reported during the study period, representing a cumulative mortality of 4.81 per million inhabitants in the general population. It was similar to that reported for the whole of Italy (4.33 per million inhabitants) [5], and in the same range as in other European countries such as Germany [15], Austria [3] and the Netherlands [3] but significantly lower than that observed in United Kingdom [16] and Greece [17].

In addition, fatal influenza cases in Sicily were mainly observed in adults (45–54 years old), which is similar to Greece [17] or Canada [13], but in contrast with other countries where the proportion of deaths was significantly higher in younger people [15,16,18]. Here we reported an overall CFR of 2.0% (range: 0.3%–17.4%), that was similar to other European studies which included in the formula the total number of ILI cases with confirmed diagnosis of pandemic influenza

A(H1N1)2009 to calculate ratios [17,19], but much lower than observed in previous pandemics [18].

Viral pathogenicity [20], improvement in nutritional status and housing, and the availability of healthcare might explain some of the apparent decrease in CFR from one pandemic to the next. It is widely believed that low CFRs in the 2009 pandemic resulted from aggressive early treatment with antiviral drugs such as oseltamivir and zanamivir, as well as major advances in intensive care medicine.

Although the number of patients admitted to ICU or managed with ECMO was higher during the 2009 pandemic compared with previous influenza seasons [21], the prevalence of Sicilian ILI patients admitted to an ICU was less than 7%. Of note, ICU admission was disproportionately higher among ILI cases negative for influenza A than for influenza A(H1N1)2009-positive cases (8.9% vs. 3.8%), although the disease was more severe and had a worse prognosis in influenza A(H1N1)2009-positive patients, including 11 of 16 ECMO treatments and all 24 deaths.

Viral or bacterial co- or superinfections of the respiratory tract have been suggested as a possible cause of severe disease, particularly *S. pneumoniae* [22]. However, the determinants for the progression of respiratory tract infections to fatal disease are still poorly understood and the findings on this topic are conflicting, and fail to demonstrate a clear and consistent involvement of other pathogens in severe complications of hospitalised patients with influenza A(H1N1)2009 [23–25]. In the present study, laboratory data on bacterial or viral co-infections in confirmed cases of influenza A(H1N1)2009 were not available to assess this hypothesis. Nevertheless, it is reasonable to assume that influenza infection may negatively interact and that underlying risk factors or comorbidities play a key role in the progression of the disease [14,15] or increase the risk of influenza-related complications [12,26].

Most (19 of 22) of the fatal cases of influenza A(H1N1)2009 in Sicily had at least one underlying risk factor, and 11 of them had more than one comorbid conditions. Recent reports have described high proportions of severe or fatal cases of influenza A(H1N1)2009 among obese patients [27], and in the fatal cases in Sicily obesity was the most common risk factor, alone or associated with other comorbidities. However, although obesity has been linked to higher all-cause mortality in large epidemiologic investigations [28], some studies in critical care settings reported that there was no correlation between body mass index and fatal outcome [29]. The pathophysiology of severe pandemic influenza A(H1N1)2009 in obese individuals is unknown, and further research is needed to elucidate the role of obesity in influenza mortality.

Finally, pregnancy has recently been identified as a noteworthy risk factor [12]. In our study population, only one pregnant woman was affected by influenza A(H1N1). She required rescue therapy by ECMO for severe pulmonary complications. This patient had no other underlying risk factors.

Our study is subjected to several limitations. Firstly, clinical and epidemiological data were not extracted from standardised medical records but from questionnaires provided with biological samples, that did not systematically include information about influenza-related risk factors. Secondly, it must be stressed that the estimated PMR could be liable to uncertainty because of the limited number of laboratory-confirmed fatal cases of influenza A(H1N1)2009. However, a number of deaths due to influenza A(H1N1)2009 may have remained undiagnosed.

In conclusion, the most vulnerable groups for pandemic influenza virus infection in our setting were younger people, and women were, at least in older age groups, more prone to illness. Deaths occurred in adult individuals with pre-existing risk factors, most frequently obesity. In the near future, more studies should be focused on the prevalence of co-existing or secondary bacterial or viral infections in hospitalised patients admitted with severe ILI symptoms, associated with confirmed influenza virus infections, to better define the role of influenza viruses in the severity of the disease and ultimately support prevention programmes such as vaccination, especially in particular risk groups.

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