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Deaths due to pandemic influenza A (H1N1) 2009 in Portugal

From April 2009 to March 2010

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SUMMARY

We have carried out the analysis of the 124 deaths due to pandemic influenza A (H1N1) 2009 reported in Portugal for the period from April 2009 to March 2010. The estimated mortality rate was 1,17 per 100.000 inhabitants. About 60% of the fatal cases were male, mean age was 47,6 years and 66,7% had at least one risk factor for severe disease. Chronic lung and heart diseases were the most prevalent risk factors identified in 24,7% and 20,7% of cases, respectively. More than three quarters of patients were hospitalized in intensive care units (ICU). Primary viral pneumonia was the leading cause of death, diagnosed in 79,7% of patients. We have found statistically significant differences in the distribution of cause of death in groups of individuals with and without risk factors (p=0,048). Our estimate of the potential years of life lost was 2853 years, with a rate of 30,8 years per 100.000 inhabitants.

The values found are in general comparable with those found in other countries with the same level of development. In future similar circumstances the compulsory notification of confirmed cases of high severity should be considered.

Keywords: pandemic influenza, deaths, mortality.

INTRODUCTION

In April 2009, the increase influenza activity reflected in respiratory infections in Mexico and California was associated with the identification of a new strain of influenza virus designated later by A/California/4/2009 A (H1N1) 2009. The spread evolution of this virus was very fast, and reached all continents in only a few weeks.

Portugal activated the Contingency Plan[(1)] for pandemic influenza on April 24, 2009 and remained in containment phase until August 21, 2009. The first diagnosed case in the country occurred on April 29. During the containment phase there were 2046 laboratory confirmed cases.

In Portugal, like in other countries, there were deaths associated with influenza A (H1N1) 2009. The first death occurred on September 23, 2009 and the last on March 3, 2010. With the current epidemiological analysis of the A (H1N1) 2009 confirmed deaths reported in Portugal, we intend to contribute to the better knowledge of the characteristics of infection with influenza A (H1N1) 2009, so that the level of response for future pandemics can be improved.

OBJECTIVES

To characterize the observed deaths due to pandemic influenza, according to sex, age group, time of death, geography, risk factors for severe disease, admission to ICU, causes of death and to estimate the rate of mortality and potential years of life lost.

MATERIAL AND METHODS

All deaths were confirmed by laboratory testing by RT-PCR. A database with all reported pandemic influenza deaths was created by the Directorate General of Health (DGS) and subsequently validated by phone, email or through visits of representatives of the DGS to hospitals.

We have considered the following classification for the risk factors for severe disease in the course of infection with influenza A (H1N1) 2009[2]:

1. No risk factors
2. Pregnancy/puerperium (≤15 days after birth)
3. Chronic lung disease (e.g. asthma, COPD, cystic fibrosis)
4. Chronic kidney disease
5. Chronic heart disease (excluding hypertension alone)
6. Chronic liver disease
7. Chronic hematological disease (e.g. hemoglobinopathies, excluding neoplasms)
8. Chronic neurological/neuromuscular disease
9. Chronic metabolic disease (e.g. diabetes)
10. Malignant disease (e.g. solid and hematological tumors)
11. Immunosuppression (e.g. congenital, associated with HIV infection and organ transplantation, post chemotherapy, immunosuppressive doses of corticosteroids)
12. Morbid obesity (<10 years: BMI ≥25, ≥10 and ≤18 years: BMI ≥ 35, >18 years: BMI ≥ 40)
13. Chronic therapy with salicylates in patients aged <18 years

We have considered the following causes of death:
1. Viral infection, including primary viral pneumonia and other forms of viral infection (e.g. encephalitis or myopericarditis)
2. Secondary bacterial pneumonia (concomitant or sequential to the viral infection and not transmitted while in hospital)
3. Decompensation of co-morbidity
4. Complications or problems during hospitalization (e.g. bleeding, stroke, pulmonary

For the estimate of mortality rates we have used the estimated Portuguese resident population on 31/12/2008[3] according to the National Statistical Institute (INE). The residence region of the fatal cases was classified according to NUTS II, 1999 (Nomenclature of Territorial Unit, 1999)[3]. For the estimate of the potential years of life lost we have used the age limit of 70 years[4,5,6,7].

For data analysis we have used PASW Statistics® version 18 and Microsoft Excel 2003. To compare the mean ages we used the T-Student and Anova tests. To evaluate the association between the causes of death and the presence of risk factor we have used Fisher's Exact test. We have considered as non-significant all differences whose *p-value* was above 0,05.

RESULTS

Portugal reported 124 deaths due to pandemic influenza. With the exception of one death, which occurred at home, all others (123; 99,2%) occurred in hospitals of the National Health Service. The total number of deaths corresponds to a mortality rate of 1.17 per 100 000 inhabitants. There were no A (H1N1) 2009 confirmed deaths among healthcare workers.

Age and gender

The deaths occurred in 74 males (59,7%) and 50 females (40,3%). The average age was 47,6 years, median 49, with no statistically significant difference (p=0,873) between the gender, whose mean and median ages were respectively 47,9 and 50 years for males and 47,3 and 47 years for females. The minimum age was 5 months and maximum 88 years. We have found that almost half of the deaths (46.8%) were aged between 45 and 64 and about ⅓ (35,5%) between 15 and 44. Only 16 (12,9%) of deaths occurred in the group aged ≥ 65 years (Table I).

Age group and gender	Nº (%)	Mortality rate/10^5 inhabitants
Age group		
00-04 years	2 (1,6)	0,38
05-14 years	4 (3,2)	0,37
15-64 years	102 (82,3)	1,43
- 15-44 years	*44 (35,5)*	*1,00*
- 45-64 years	*58 (46,8)*	*2,13*
≥65 years	16 (12,9)	0,85
Gender		
Male	74 (59,7)	1,44
Female	50 (40,3)	0,91
Total	124 (100)	1,17

Table I - Distribution of confirmed A (H1N1) 2009 deaths by age group and gender, and mortality rate per 100.000 population, from April 2009 to March 2010, Portugal. (Source: DGS)

Time distribution

The highest number of deaths (57, 46% of the total number) occurred in December 2009. There was a two weeks lag between the peak of weekly distribution of consultations for influenza-like illness and the peak week of A (H1N1) 2009 deaths, which ocurred at weeks 49 and 50 (November 30 to December 13) with 16 deaths (Figure 1).

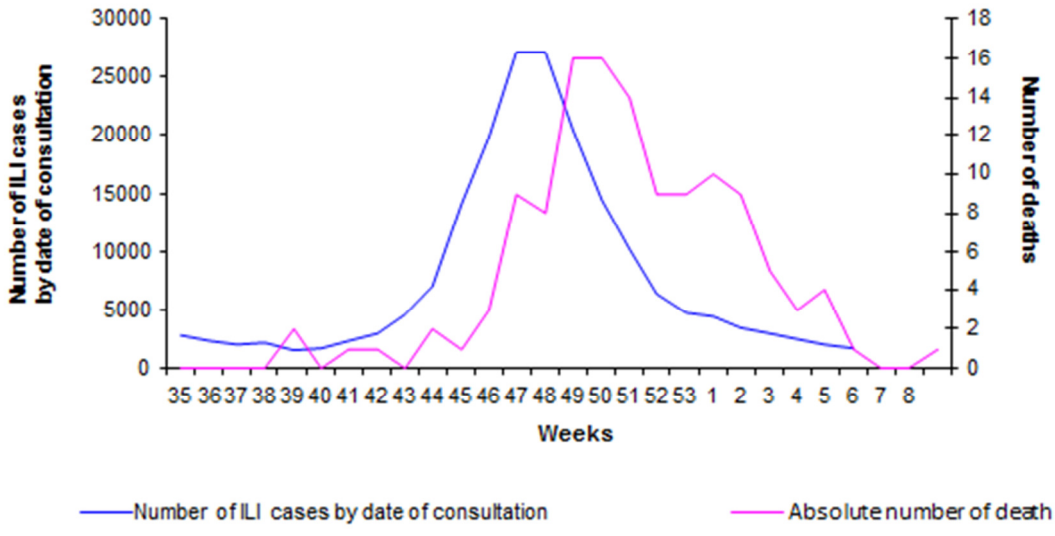

Figure 2 - Number of ILI cases and deaths due influenza A (H1N1) 2009 per week, from April 2009 to March 2010 in Portugal. (Source: DGS)

Region of Residence

Next table shows the mortality by region of residence, noting one death of a Portuguese citizen living outside of Portugal and one of a foreign citizen non-resident in our country (Table II).

Region of residence	Number of deaths	Mortality rate/10^5 inhabitants
Mainland	106	1,05
Northern Region	*45*	*1,20*
Central Region	*26*	*1,45*
Region of Lisbon and Tagus Valley	*29*	*0,79*
Alentejo Region	*4*	*0,79*
Algarve Region	*2*	*0,47*
Autonomous Region of Madeira	13	5,26
Autonomous Region of Azores	3	1,23
Portugal	122	1,15
Foreign countries	2	-

Table II - Distribution of deaths in Portugal due to influenza A (H1N1) 2009 and mortality rate per 100.000 inhabitants, by region of residence (NUTS II 2009), from April 2009 to March 2010. (Source: DGS)

Risk factors

We ignore the existence of risk factors in one of the deaths (autopsy findings in secrecy). We have found that 82 (66,7 %) of the 123 studied deaths had at least one risk factor for severe disease. The average age of these patients was 48,5 years, higher than the 46,8 years of those without risk factors (n=41; 33,3%), but without statistical significance (p=0,621). Note that 52 (63,4%) of the 82 patients with risk factors had only one risk factor and 30 (36,6%) had more than one. It was found that 6 (7,3%) cases with three or more risk factors were aged over 45 years. In children, aged under 18, all the fatal cases had at least one risk factor. The presence of risk factors was found in 68,8% of the patients aged ≥65 years and its lowest expression (56,8%) in patients with ages between 15 and 44 years.

Chronic lung and heart diseases were the most prevalent risk factors identified, respectively, in 20 (24,7%) and 17 (20,7%) patients, followed by immunosuppression, present in 16 (19,5%) cases (Table III). In paediatric patients the most frequent risk factor was neuromuscular disease, present in four (66,7%) deaths.

Risk factors	Nº (%)
Chronic lung disease	20 (24,7)
Chronic heart disease	17 (20,7)
Immunosuppression	16 (19,5)
Chronic metabolic disease	15 (18,3)
Oncological disease	14 (17,1)
Chronic neurological/neuromuscular disease	14 (17,1)
Chronic liver disease	11(13,4)
Morbid obesity	8 (9,8)
Chronic kidney disease	4 (4,9)
Pregnancy/puerperium	1(1,2)

Table III - Number and percentage of deaths due to influenza A (H1N1) 2009, according to the risk factor, from April 2009 to March 2010 in Portugal. (Source: DGS)

Morbid obesity was present in 8 (9,8%) cases. The non-morbid obesity, with BMI between 30 and 40, was present in 18 patients, 12 of whom without risk factors. In the group of chronic metabolic diseases only diabetes mellitus was identified. From the 14 cases with neurological disease or chronic neuromuscular, three had Down's syndrome.

Admission to ICU

We verified that 95 (77,2%) of the 123 hospitalized patients were admitted to ICU and 94 (98,9%) of these patients were submitted to invasive mechanical ventilation, three have been submitted to ECMO (Extracorporeal Membrane Oxygenation). We were unable to identify the number of patients submitted to renal replacement therapies.

Cause of death

The cause of death is unknown in one case as the autopsy report is under investigation by legal authorities. Primary viral pneumonia, diagnosed in 96 (79,7%) of the 123 patients, was the most frequent cause of death, followed by complications during hospitalization and decompensation of comorbidity, occurring respectively at 8,1 and 6,5% of cases. Secondary bacterial pneumonia was diagnosed in only 4 (3,3%) of the cases (Table IV).

The distribution of cause of death by according to the presence and absence of risk factors was statistically significant (p=0,048). However, we found no statistically significant difference between each of the causes of death when compared with all the others, although the decompensation of comorbidity presented a marginal significance (p=0,051).

The most reported cause of death in the 6 persons aged <18 years was primary viral pneumonia, in 5 (83,3%). The other death cause was decompensation of chronic respiratory disease.

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Cause of death	Total Nº (%)	No risk factors	With risk factors
Viral infection:	101 (82,1)	36 (87,8)	65 (79,2)
- Primary viral Pneumonia	*98 (79,7)*	*34 (82,9)*	64 (78,0)
- Encephalitis and/or myopericarditis	*3 (2,4)*	*2 (4,8)*	1 (1,2)
Complications	10 (8,1)	5 (12,2)	5 (6,1)
Decompensation of comorbidity	8 (6,5)	0 (0)	8 (9,8)
Secondary bacterial pneumonia	4 (3,3)	0 (0)	4 (4,9)
Total	123 (100)	41(100)	82 (100)

Table IV-Number and percentage (descending order) of the deaths due to influenza A (H1N1) 2009 according to cause of death, in total and by presence or absence of risk factors, from April 2009 to March 2010, Portugal. (Source: DGS)

Years of potential life lost

We have estimated a value of 2853 years of potential life lost, with a rate of 30,8 years per 100.000 inhabitants. The average number of years of potential life lost for each dead patient was 23 years.

DISCUSSION

This study covers the 124 influenza A (H1N1) 2009 deaths reported with laboratory confirmation of the diagnosis by RT-PCR. Although the pandemic influenza infection was not a mandatory reported disease, there was a great effort of the National Health Service for the diagnosis of the infection and the report of all fatalities. However, we must consider that more deaths may have occurred, including cases where the diagnosis was not suspected, and therefore were not sent for laboratory confirmation, or false negative results due to technical problems in sampling or resulting from the diagnostic yield of the laboratory tests. Despite these limitations, also reported in similar studies, we assume that the DGS database is reliable and covers, if not all, the vast majority of deaths in Portugal.

It is the first time in flu pandemics that only the deaths with laboratory confirmation are considered for analysis, which may explain discrepancies on comparing the impact of previous pandemics. Similarly, laboratory confirmation is not used in the assessment of mortality during the annual epidemics of seasonal influenza.

The 124 deaths reported correspond to a mortality rate of 1,17 per 100.000 inhabitants, about one third of the value estimated by ECDC (up to 3 per 100.000) for the "worst reasonable scenario"[8]. This value of specific mortality, although higher than the average rate in the European Union[9], is within the ranges of reference for this region and is also higher than the estimated rate in the United States of America (USA) 0,97/100.000[10].

Without the total number of infected and symptomatic patients is not possible to estimate the overall case fatality rate and the case fatality rate for symptomatic illness cases. In the U.S[11] and United Kingdom[12], the case fatality rate for symptomatic illness was estimated, respectively, at 0,048% and 0,026%.

According to the DGS Report of Pandemic Influenza in Portugal[13], 1 436 hospital admissions were reported, with 193 admitted to UCI, representing a 13.4% ICU admission rate and a intra-hospital and intra-ICU mortality rate of 8.6% and 49.2%, respectively. We believe that these values must be evaluated carefully and may not reflect the national reality, given the lack of mandatory reporting and the subsequent underestimation of the number of hospital admissions. Extrapolating from previous studies[14,15,16,17] it is acceptable to estimate 2400 hospital admissions and 300 ICU admission in Portugal during the pandemic A (H1N1) 2009. In several published studies it was documented that between 9 and 31% of the hospitalized patients required admission to ICU, and 14 to 46% of those patients have died[14,17,18,19,20].

The average age of fatal cases was 47,6 years with a small male predominance (59,7%) without significant differences between the average ages of both sexes. The age group between 15 and 64 years was the most affected and the subgroup between 45 and 64 years in particular, with a mortality rate of 2,13/10^5 inhabitants. The predominance of males has been documented elsewhere, notably in Europe, for example, in France[21] (57%) and the Netherlands[22] (55%). The involvement of younger age groups is also in conformity with what was verified in other studies, being the average age of the fatal cases in the UK[23] 43 years and 52 years in the Netherlands[22]. In Portugal, 87,1% of deaths occurred in individuals younger than 65 years, supporting the overall estimate that approximately 90% of the deceased were younger than 65 years[24]. This finding contrasts significantly with the values found in seasonal influenza, where more than 80% of deaths in our country occur in people aged over 75 years[25].

The weekly distribution of deaths in Portugal followed the weekly distribution of consultations for influenza-like illness with a time lag of two weeks which is also in accordance with the expected[8].

The variation found in the mortality rates by regions of Portugal must be interpreted with caution considering the small number of deaths and the demographic variations between regions. However, other explanations have also been reported in the literature, for example, population density, higher prevalence of comorbidities, alcoholism and smoking, different conditions of access to health services, and possibly, not identified genetic factors [24].

It has been estimated that 25 to 50% of the deaths had no risk factors[24] for pandemic influenza. In Portugal, 33,3% of deaths occurred in individuals without risk factors, when in the UK[23] this value was 23%. Although the values found in our country are between the reference ranges, the differences found may have been partly influenced by non-uniformity of methodologies and the different valuation of certain risk factors such as, for example, obesity. In this analysis, we have considered only the morbid obesity (BMI ≥ 40 in adults and the corresponding value at ages ≤ 18 years) as a risk factor. The use of non-morbid obesity (BMI ≥ 30 in adults), would decrease to 23,6% the percentage of patients without risk factors. The distribution of risk factors found in the Portuguese population is comparable to what is internationally described, with the exception of pregnancy and puerperium. In Portugal only one patient has died in these circumstances (0,8% of the total deaths) and in the international literature the values described are between 6 and 9%[17,20]. The current study does not suggest the reasons for this difference. As mentioned before, all deaths in children had at least one risk factor and almost half (43,2%) of the death cases between 15 and 44 years of age had no risk factors. In the UK, the fatal cases between 25 and 44 years presented also an highest percentage (32%) of absence of risk factors[23].

Primary viral pneumonia (*diffuse viral pneumonitis*) was the leading cause of death (79,7%), regardless of age group and the presence or absence of risk

factors. However, there is a significant difference in the distribution of causes of death in individuals with and without risk factors, which could only mean that the comorbidities are risk factors that may also constrain the cause of death (decompensation of comorbidity). The high percentage of death cases with primary viral pneumonia usually associated with ARDS (Acute Respiratory Distress Syndrome), severe hypoxemia, septic shock and renal failure, is consistent with what is described in other studies, for example, in Australia[17] and Canada[20] and may explain the high number of patients undergoing mechanical ventilation and, possibly, some complications and problems (8,1%). Despite the anticipated increase in admissions, there was no reference to shortage of beds in intensive care units. Note also, for the first time nationally, the registration of the planned use of ECMO in nonsurgical patients, which constituted a significant opportunity for innovation.

Data from other studies point to a rate of 26 to 38% of deaths from bacterial pneumonia[17,20,26,27]. In our data, this figure stood at 3,3% and is not possible with the information available to explain this disparity, although the diagnostic yield of microbiological tests and antibiotic therapy prior to sampling may be two of the factors involved.

Using a metric based on years of potential life lost allows us to scale the impact of a different pattern of mortality based on age, which is not measured by the absolute number of deaths[28]. Thus, in Portugal the number of years of potential life lost was 2853 years, which corresponds to 30,8 years per 100.000 inhabitants, allowing a complementary vision of the recorded 124 deaths.

CONCLUSION

Values found in this analysis of deaths due to pandemic influenza A (H1N1) 2009 in Portugal are comparable in general with those found elsewhere with the same level of development. However, in future public health crisis should be looked at the possibility of mandatory reporting of severe cases as, for example, those requiring admission to a ward and/or ICU in order to a better epidemiological, clinical and management resources characterization.

The analysis of potential years of life lost must be a variable to include, whenever possible, in assessing the impact of diseases with epidemic characteristics due to their increased magnitude in relation to the absolute number of deaths.

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