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SPATIAL PATTERNS OF SMRS DUE TO THE VIRUS A(H1N1)PDM09 DURING THE PANDEMIC IN GREECE IN 2009 – 2010

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Abstract

This paper aims to study the spatial structure of deaths due to the A(H1N1)pdm09 swine virus in Greece in order to identify vulnerable and resilient regions. The study period refers to the school year 2009-2010 when a swine flu pandemic took place affecting large numbers of the population including students. The deaths due to the A(H1N1)pdm09 virus have been recorded in Greece by the Hellenic Centre for Disease Control and Prevention (HCDCP). Based on these deaths and the 2011 Census for Population statistics, we calculated the Standardized Mortality Ratios (SMRs) as well as the A(H1N1)pdm09 age-specific death rates. The statistical significance of SMRs was evaluated using a chi-square test, while Empirical Bayesian procedures were employed to smooth the observed standardized mortality ratios. The geography of the analysis refers to the 13 administrative regions in Greece (EU NUTS II). The results are interesting, and the spatial patterns suggest significant inequalities in the SMRs across these regions. At the same time, we discuss the possible failure of the vaccine coverage, especially in regions where our study revealed most affected, in order to help policymakers to be better prepares for a future epidemic.

Keywords: *Pandemic A(H1N1)pdm09, Standardized Mortality Ratio, Regional Analysis, spatial analysis, empirical Bayesian Smoothing*

1. INTRODUCTION

1.1 Characteristics of A(H1N1)pdm09

According to the European Centre for Disease Prevention and Control (ECDC, 2017), the first cases of A(H1N1)pdm09 were reported in California (in March 2009) while the first severe cases of the disease were noted in Mexico in April of 2009 (Perez – Padilla et al., 2009). On 11 June 2009, the World Health Organization (WHO) declared that the epidemic had turned into the phase 6 indicating a pandemic alert (Chan, 2009). Approximately 12,469 deaths occurred in the United States of America, most of them (87%) took place during the period from 12 April 2009 to 10 April 2010 and concerned people aged 65 or more years old (Shrestha, 2011). At US level, pandemic influenza mortality slants to younger people than seasonal influenza (Nguyen, 2013). At EU level, the project known as the European monitoring of excess mortality was responsible for recording mortality data (ECDC, 2010). In Greece, the first patient was a 21-year old man, who developed a mild influenza-like form of illness on May 24, 2009 (Panagiotopoulos et al., 2009).

One interesting finding of this pandemic is the high mortality of the cases of children and younger people (5 – 14 age group) who normally would survive from an infection of another flu virus (Mazick, 2010). However, it is beyond the scope of this paper to study the demographic characteristics of the cases and deaths. According to an epidemiological study regarding the pandemic in Greece, the average age of patients in a sample of 13,939 confirmed cases was 21 years and the average age of death 53 years in the period from October 2009 to May 2010 (HCDCP, 2010). These estimates significantly underestimate the true number of cases of the epidemic A(H1N1)pdm09, since most patients had mild symptoms and there was no need for confirmation of the virus by a laboratory. During the above study period, the epidemic was at its peak during the 48th to the 49th week of 2009 when approximately 750 – 1,500 new cases in every 100,000 residents per week were recorded (Maltezou, 2011). It is estimated that the clinical rate of infestation was higher for children and young people aged 5-19 years old (range 27-57%), whereas it was lower for people aged 64 years old and over (range 0.65-2.20%). It is estimated that about 19.7% of the Greek population was infected (range 13.3-26.1%), while the case fatality rate (CFR) was 6.3 in every 100,000 infections (HCDCP, 2010).

Our study reports the Standardized Mortality Ratio (SMR) as well as its Bayesian smoothing at a regional level in Greece, in order to identify the most affected regions in the Greek territory and we make recommendations for policymaking.

1.2 The role of Mitigation Strategies

The influenza pandemic of 2009 had a serious impact on the health of the population residing in Greece (Ministry of health and social solidarity, 2009). From its outbreak in April 2009 until May 2010, the Hellenic Centre for Disease Control and Prevention (HCDCP) recorded 18,230 cases of infected patients and 142 deaths due to the swine flu (HCDCP weekly report May 26, 2010; ECDC, 2010). There are diverse studies on the pandemic outbreak and its implications. However, little attention has been paid to the spatial structure of the phenomenon. Despite the announcement of the WHO in the summer of 2010 that the pandemic was over, in Greece, deaths due to the swine flu virus, continue to be high in recent years. The latter finding motivates this study, one purpose of which is to raise awareness of the problem to the national and regional authorities in Greece.

Regions, especially those found to have a high SMR in the last swine flu epidemic, should develop action plans complementary to those developed by the national government, in order to prevent the spread of future influenza and provide support to those who would be infected. It is worth mentioning that flu pandemics cause a significant social burden, create tremendous costs and are likely to recur in the future (Germann, 2006). In the WHO final report on how to deal with the A(H1N1)pdm09 flu, it was stated that people continued to be unaware of how to cope with a serious flu pandemic or with any other global event persistent and threatening to public health (WHO, 2013). “Control strategies do not aim at interrupting transmission but in limiting morbidity and mortality.” (Hollingsworth p.1, 2011). Recent epidemiological studies of Influenza A(H1N1) have shown that the earlier a long-term intervention is launched, the higher the profitable reaction will be according to the magnitude and maximum persistence of the epidemic (Hollingsworth, 2011). An early intervention has two significant arguments in favour: a) firstly, the epidemic peak occurs thereafter in cases of early interventions, thus allowing time for the preparation of public health facilities and the manufacturing of a strain-specific vaccine, and, secondly, that it is precisely in the early stages of an outbreak that there is great ambiguity about its severity (Garske, 2009; Hollingsworth, 2011). Corresponding, non pharmaceutical interventions were also noted in Mexico during the Pandemic A(H1N1)pdm09 (Stern and Markel, 2009). Policymakers point out the importance of integrating "conservation, health and family planning interventions" (Carr et al., 2017). Unfortunately, no comparison can be made between countries due to a lack of standardization among national supervision systems (Briand et al., 2011). As a result, the findings of the spatial variation of Standardized Mortality Ratios (SMRs) among a country's regions informs policymakers allowing them to make decisions about the appropriate interventions.

Being vaccinated constitutes one of the most important prevention measures of the flu from the virus A(H1N1)pdm09 (Jennings et al., 2008). Particularly, as WHO stated, health care workers are considered "first priority" and must be vaccinated against the virus A(H1N1) (WHO, 2010). Various studies that examined the percentage of health professionals who wished to be vaccinated against the seasonal flu proved a very low level of vaccination among those at risk. For example, the percentage documented in the UK was 14%, in France it was 48%, and in Hong Kong, it was 47% (National Seasonal Influenza Vaccination Survey in Europe, 2008). A low percentage of those wanting to be vaccinated (17%) was also recorded in Greece (Rachiotis et al., 2010). The variable level of vaccination among healthcare professionals across the EU had an impact on the vaccination of the population (ECDC, 2009). The combination of the low percentage of vaccinated health professionals and the hysteria formed in the general public via media, which was not an official opinion of specialists, led to a dismal percentage (3%) of the entire population vaccinated in Greece (Tsoucalas and Sgantzos, 2016). It is necessary to note that vaccinations constitute a cornerstone since they play an important role in the proper functioning of the healthcare system which during a pandemic is to the population's benefit.

2. DATA AND METHODS

2.1. Data

The source of data analysed here is the Hellenic Centre for Disease Control and Prevention (HCDCP) which publishes weekly reports on epidemics and has been responsible for the epidemiological surveillance of the flu during the period 2009 - 2010. The HCDCP also reports to the European Centre for Disease Prevention and Control (ECDC). All reports and relevant material are available online at the official website of HCDCP (http://www.keelpno.gr). It is necessary to note that the HCDCP reported 149 deaths for the period 2009 – 2010 in their weekly report and ECDC, while the official data provided to us at the regional level after a formal request, add up to 142 deaths of the same period. To avoid confusion, the 149 deaths refer to a whole year from April 2009 to summer 2010 (this is the period of the pandemic according to the WHO), while the 142 deaths refer to the "academic year" from week 40 (early October) of 2009 to week 20 (late May) of 2010 of the following year. In order to calculate the SMRs, we analysed total population by age at the regional level of geography (EU NUTS II) the source of which is the 2011 Census for Population in Greece conducted by the Hellenic Statistical Authority (ELSTAT). The SMRs were calculated using the national age-specific deaths rates from A(H1N1) in 2011 using as standard the age mortality rates of death indicators of the total population of the country in 2011 (ELSTAT, 2011).

2.2. Methodology

Even though the new flu was considered less severe, in Greece from October 2009 to May 2010, 142 deaths were officially recorded (Sypsa, 2011). The statistical significance of the corresponding Standardized Mortality Ratios (SMRs) was evaluated based on the appropriate Chi-Square (χ^2) test (Kalogirou et al., 2012). Moreover, the indirect SMRs were calculated for each of the 13 regions in Greece, based on the evidence gathered by the HCDCP from the disease outbreaks in 2009. Additionally, Bayesian Analysis procedures were implemented to smooth the observed SMRs as they are affected by the relatively small numbers of the events registered. Detecting mortality differentials between regions is an important first step towards elaborating and pursuing suitable policies which can result in a reduction in fatalities, in the event of a new resurgence of the A(H1N1)pdm09 flu, as has been conducted regarding other causes of deaths (Verropoulou and Tsimbos, 2015).

It is a common practice by public health professionals to compare levels in order to identify patterns of mortality among different geographical areas. When the registered numbers of events are inadequate to calculate age-specific death rates at the regional level, indirect standardization techniques are used to allow for meaningful comparisons. The Standardized Mortality Ratio (SMR) is one of the most commonly used measures of mortality in regional mortality analysis (Julious, 2001; Tsimbos and Papadakis, 2004) and it is calculated by using the following formula (Waller and Gotway, 2004):

$$SMR = \frac{O}{E} \times 100 = \frac{O}{\sum M_x \cdot p_x} \times 100 \quad (1)$$

where O is the observed number of cases, E is the expected number of cases calculated by applying a set of standard age-specific mortality rates (M_x) to the observed age distribution of the study population (p_x). The SMRs show whether the average mortality rate of a specific population is larger or smaller than that in the standard population. Thus, two (or more) indirectly standardized death rates are not comparable. Having as an objective to estimate and perform statistical inference of SMRs, we can achieve it in the following two ways (parametric and Bayesian).

One of the first and most important models of evaluation for SMRs is the assumption of the Poisson distribution. The assumption underlying the use of a Poisson distribution concerning the deaths recorded may not always be true. More specifically, the fact that in the Poisson distribution, the mean is equal to the variance can cause problems to the analysis. The variance observed is often greater than the variance assumed in our model, and as a result, in this particular situation, the variation is larger than the mean. As a solution to this problem, we can use the Empirical Bayesian Smoothing method, which is inferred from the data. The latter means that SMR shrinks towards the total mean, which is designated as posterior distribution and is a random variable. The aim of using the Bayesian Smoothing method (Clayton and Kaldor, 1987) is to get estimates for the posterior distributions of relative risk from the marginal likelihood of the deaths observed (O_i). The mean can be calculated and is designated as empirical Bayesian Smoothing of relative risk and is given by the following formula:

$$E[SMR_i | O_i, \alpha, \beta] = \frac{O_i + \alpha}{E_i + \beta}, \qquad (2)$$

where the parameters α and β will be estimated by the method of moments (Marshall, 1991). The model which will be used in the current assignment is Gamma-Poisson. The combination of Gamma distribution with the Poisson probability density function (Gamma-Poisson model) provides a prior density of the relative risk, which is also defined as Gamma (Gelman et al., 2004) proved that marginal distribution follows the negative binomial distribution.

Before we conduct any further analysis on the presence of spatial autocorrelation, we must evaluate the heterogeneity of the respective risks. We can determine if there are any true differences among the different relative risks (Bivand et al., 2013). The Chi-square statistic is given from the following formula.

$$X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}, \quad (3),$$

where O_i is the observed deaths of region i and E_i the expected deaths for region i.

Since the expected and observed number of deaths have been calculated for each region in Greece, the chi-square shown in Eq. 3 above can be also calculated (Bivand et al, 2013). The null hypothesis indicates non-statistically significant differences. As a result, rejecting the null hypothesis means that there is a statistically significant difference between the observed and expected deaths. In order to check the existence of spatial autocorrelation, we computed the classic *Moran's I* (Moran, 1950) statistics using the formula below (Cliff and Ord, 1973; Cliff and Ord, 1981; Kalogirou, 2015):

$$I = \frac{n}{\sum_i^n \sum_j^n w_{ij}} \cdot \frac{\sum_i^n \sum_j^n w_{ij}(O_i - \bar{O})(O_j - \bar{O})}{\sum_i^n (O_i - \bar{O})^2}, \quad (3)$$

where n is the number of observations; O_i, O_j are the observed deaths in the regions i and j, respectively; $\bar{O}$ is the mean of the observed deaths; and w_{ij} are the weights defined by the selected spatial kernel. The weighting scheme used here refers to binary weights using an adaptive kernel with three nearest neighbours (k = 3). This is due to the low number of observations (13 regions) and the fact that islandic regions have no physical neighbours.

3. RESULTS

3.1. Indirect Standardized Incidence rates and SMRs

The results suggest a high level of regional inequality and interesting spatial patterns. We first report the indirect standardized incidence rates per 100,000 population for Greece and each of the 13 Regions (Figure 1). The rates range 308 per 100,000 population with the highest rate observed in the Region of Crete (333) and the lowest in the Region of Western Macedonia (25). The rate for Greece is 169 per 100,000 population leaving seven regions below the national rate and six above it. Lower incidence rates are observed in the Regions of South Aegean (excluding Crete), Western Greece, Peloponnese, Central Greece, Central Macedonia, Eastern Macedonia and Thrace and Western Macedonia (with the lowest rate of cases confirmed). In addition to Crete with 333 cases per 100,000 residents (double the national rate), the Regions of the Ionian Islands (269 cases per 100,000), Northern Aegean Islands, Epirus, Attica and Thessaly have a higher than the national rate.

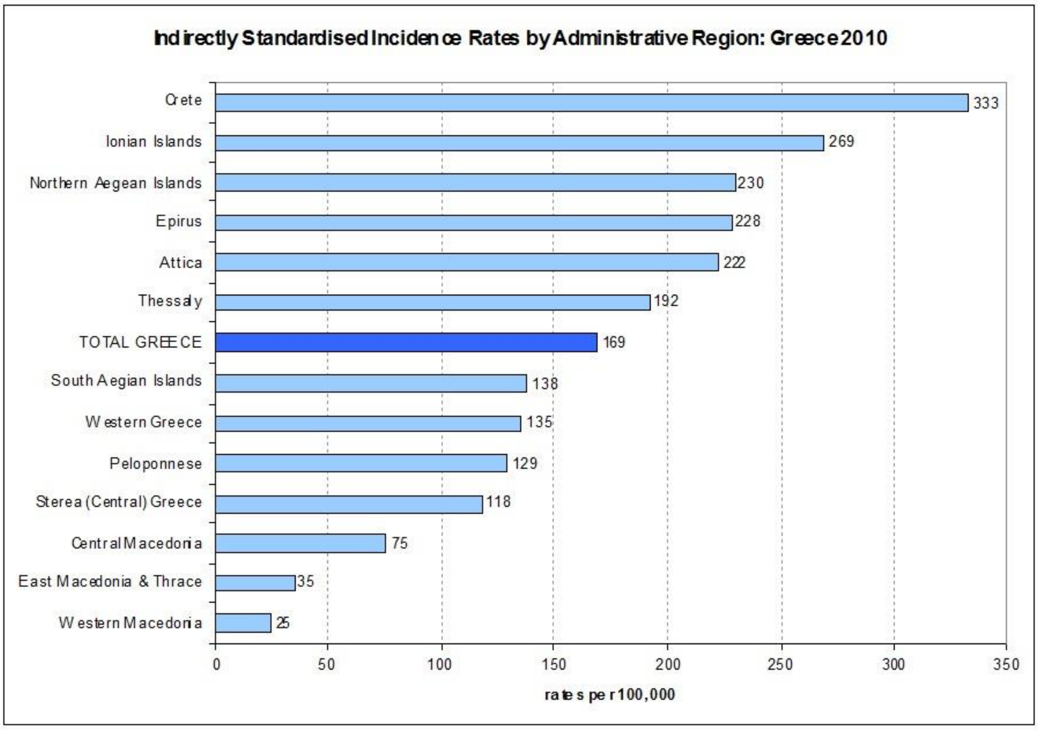

Figure 1: Indirect standardized incidence rates by region per 100,000 population: Greece 2010

Table 1 shows the observed number of deaths, the SMRs and the Chi-square statistic for each Region in Greece. By ordering the values from the highest to the lowest SMR, it can be demonstrated that the four Regions with the lowest mortality are Central Greece, Attica, Northern Aegean Islands and Epirus whereas the four regions with the highest mortality include the Peloponnese, Central Macedonia, Southern Aegean islands and Thessaly. At 1% level of significance, we can see that in two regions the SMRs are statistically significant, namely in Thessaly and in Attica.

Table 1: Observed deaths from H1N1, Standard Mortality Ratios, (SMR) and Chi-Square test.

ADMINISTRATIVE REGION	OBS	SMR	Chi Square
Thessaly	22	224	15.01
Southern Aegean Islands	7	182	2.57
Central Macedonia	35	141	4.16
Peloponnese	9	115	0.17
Western Macedonia	4	104	0.01
Western Greece	9	102	0.00
East Macedonia & Thrace	8	99	0.00
Crete	7	90	0.08
Epirus	4	87	0.07
Northern Aegean Islands	2	76	0.14
Attica	32	64	6.28
Ionian Islands	1	36	1.15
Central (Sterea) Greece	2	27	3.91

The following thematic map indicates the different values of the index SMR. The darker orange colour refers to the region of Central Macedonia that exhibits a rate of 141% (a mortality rate higher by 41% compared to the whole of the country). Regions coloured in pale orange exhibit ratios of 82% (South Aegean islands) or higher. Finally, Thessaly (coloured red) exhibits the highest SMR having a mortality rate higher by 124% compared to that of Greece.

The analysis continues with the calculation of the chi-square statistic (Bivand et al., 2013) for testing the heterogeneity of SMR. At a level of significance of 1%, the chi-square statistic assesses whether there are true differences among the different risk factors (observed and expected number of deaths) taking into account both observed and expected values. The p-value of the test equals 0.004 (< 0.01). Therefore we reject the null hypothesis concerning the equality of relative risks. We thus conclude that there is a heterogeneity (statistically significant difference) between the regions of observed and expected death values.

The SMRs of the deaths due to the virus A(H1N1)pdm09 exhibit a non-significantly negative spatial autocorrelation (Moran's I = - 0.24; p-value = 0.104) suggesting that regions with high SMR neighbour regions with low SMR. The weighting scheme used in our study refers to binary weights using an adaptive kernel with three nearest neighbours (k = 3). Increasing the number of nearest neighbours to four or five resulted in similar Moran's I values.

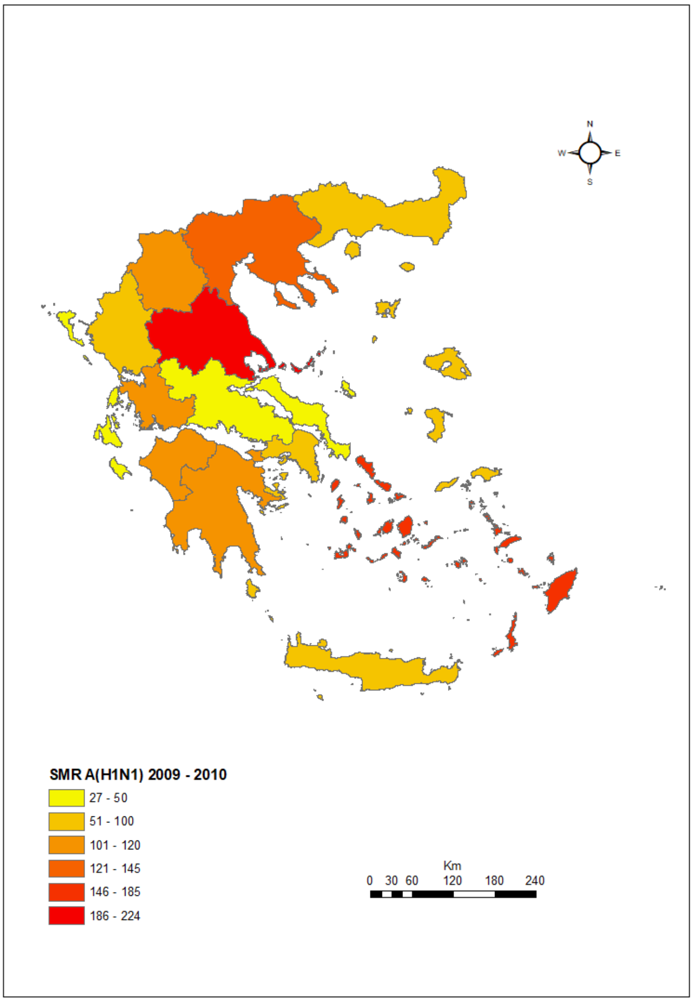

Figure 2. Mapping the SMR by region: Greece 2009 - 2010.

3.2. Bayesian Smoothing of SMR

The map presented in Figure 3 shows the smoothed Empirical Bayesian Rates for the Standardized Mortality Ratio (SMR) using a weighting scheme of three nearest neighbours. The smoothed rates are lower and nearer to the average compared to those presented in Figure 2. By sorting the values from highest to lowest (Table 2), we observe that the regions with the lowest mortality in relation to the whole country are West Greece, Crete, the North Aegean, Central Greece, the South Aegean and Epirus. We note that the regions with the highest rates are: a) the Ionian Islands (mortality rate 30% higher than the country as a whole), b) Central Macedonia with a higher mortality rate 32% and c) Thessaly with a mortality rate of 73% higher than the whole of the country. Three Regions follow with lower rates: Attica, Western Macedonia and the Peloponnese at 108%, 102% and 101%, respectively. Higher percentages of smoothed SMRs are most affected by the overall average and therefore tend to shrink by Bayesian smoothing (e.g. South Aegean, Thessaly, Central Macedonia). The primary goal of Bayesian smoothing is to eliminate as much as possible the strong variability in the standardized mortality ratio (SMR). At the same time, the lower values of the SMRs are also influenced by the overall average, and for this reason, an increase in these rates is observed, for example in Sterea Greece in the Ionian Islands and Attica. With this smoothing technique, we notice that the ranking of the regions regarding the SMR has changed. At the highest SMR level, the only difference is the replacement of the South Aegean Region with that of the Ionian Islands and the Region of Central Macedonia now holding the second place. The Region of Thessaly remained in the first place. In Figure 4 we can see how the Bayesian technique significantly reduces the observed variability of the standardized mortality ratio (SMRs) for each region. The corresponding mapping is presented in Figure 3.

It is noteworthy that the Bayesian smoothing indicators of SMR present a non-statistically significant negative spatial autocorrelation (Moran's I = -0.11, p-value = 0.45) using the weighting of three neighbours. A similar result was obtained with a different weighting scheme (neighbours k = 4, k = 5). In Figure 4 it is shown schematically how the Bayesian smoothing technique substantially reduces the observed variability of the standardized mortality ratios (SMRs) per region by not assuming equal mean and variance but using the variance of the Negative Binomial distribution. At the same time, the Bayesian technique borrows information from all the neighbouring regions.

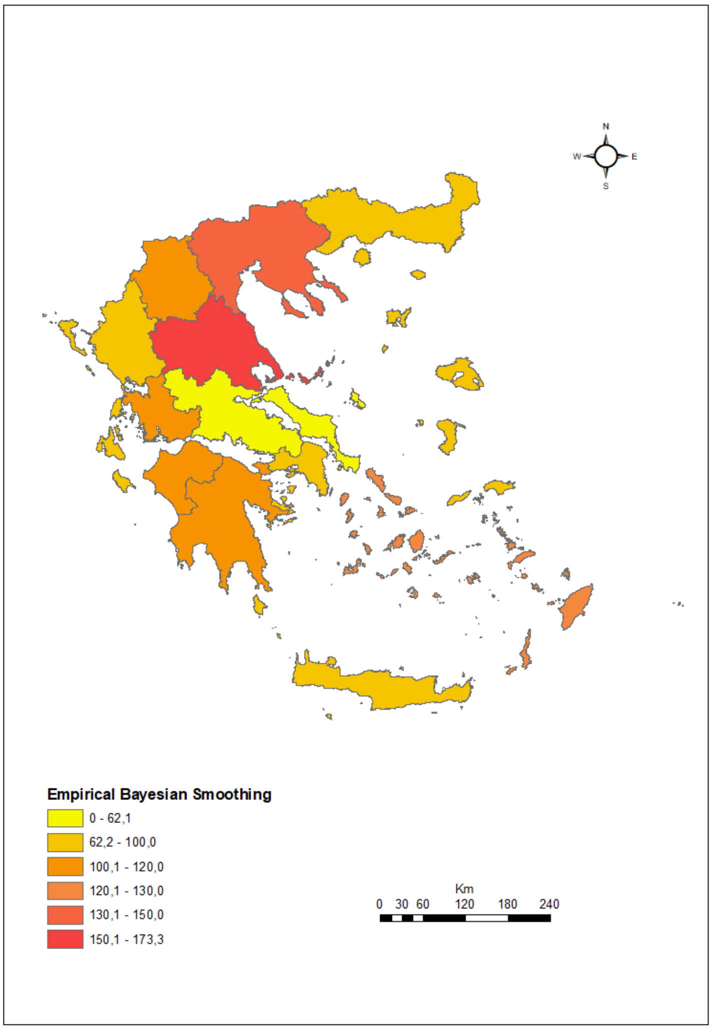

Figure 3. Map of the Empirical Bayesian Rate Smoothing for the Standardized Mortality Ratio (SMR)

Table 2: Observed and smoothed Standardized Mortality Ratios

ADMINISTRATIVE REGION	OBS	Empirical Bayesian Smoothing
Thessaly	22	173
Central Macedonia	35	132
Ionian Islands	1	130
Attica	32	108
Western Macedonia	4	102
Peloponnese	9	101
East Macedonia & Thrace	8	99
Epirus	4	95
Southern Aegean Islands	7	95
Central (Sterea) Greece	2	93
Northern Aegean Islands	2	81
Crete	7	69
Western Greece	9	62

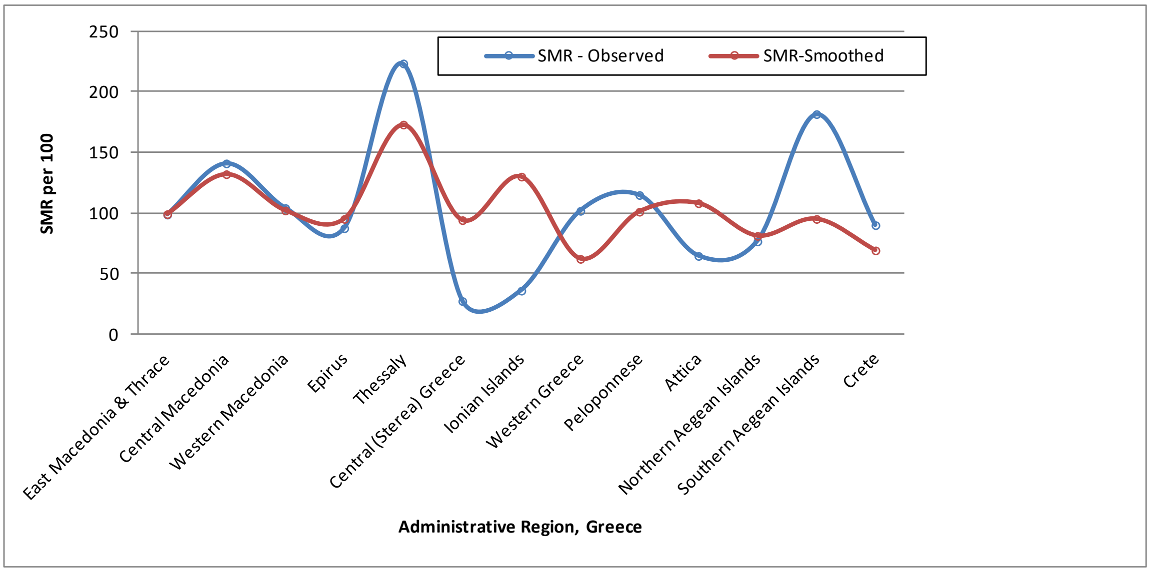

Figure 4: Observed vs smoothed (Empirical Bayesian Smoothing) SMR

4. CONCLUSION

This paper showed that during the A(H1N1)pdm09 pandemic, several regions in Greece were affected more than the country's average regarding both the confirmed cases and deaths due to the specific virus. The spatial patterns suggest spatial inequalities in the SMRs due to the A(H1N1)pdm09 virus. These findings show that there is a need for more efficient policy in a probable future pandemic of the flu to reduce the morbidity and the mortality of the population in Greece, especially at the regional level. It should be the responsibility of regional governments as well as the Ministry of Health and related stakeholders to inform and prepare the population especially the children and the elderly, on how to better prevent future epidemics or pandemics. Improving vaccination policy in Greek territory will be an asset in a future epidemic. It must be noted that only 1.18% of parents were willing to accept the vaccination program in Greece (Nikolakopoulou, 2010). Is evident the wide gap in the Greek society during the vaccination period especially when compared with studies which showed a high degree of willingness for vaccination. More specifically a study which was conducted in the USA and showed that 75% of the parents consented to be vaccinated against the virus A(H1N1)pdm09 (Julia et al., 2011). When considering the appointed percentage for the virus A(H1N1) at 33%, we realise how far is the reaching point where the population becomes immune. More specifically, since the start of the pandemic and up to 7/3/2010, 364,576 people were vaccinated in Greece, while the estimated population at high risk ranged between 1.5 and 1.7 million people.

Panagiotopoulos (2010) identified two major points of great significance. First, at the regional level, besides Crete which noted a vaccination coverage at a percentage of 10%, the other regions noted very low percentages of the vaccinated population such as 3.84% in East Macedonia & Thrace and 2.67% in the Peloponnese and Epirus. It is worth noting that Thessaly had a very low percentage of vaccination (2,89%) while our study showed that it had the highest probability of death (124%) in relation to the probability at the national level. Moreover, Panagiotopoulos (2010) concludes that a "handling of the pandemic flu A (H1N1) of 2009 brought to light the chronic institutional failures of the Health system and mistakes". The solution to this is to emphasize the "proper function of institutions". It is also worth mentioning that Greece is placed in one of the lowest rank, in comparison to other European countries, when it comes to vaccination coverage. The countries which hold the lowest positions include

Italy, Cyprus, Greece and Spain, with a percentage ranging from 1.5% to 3.4%. The highest percentages are noticed in the northern countries of Europe which are: Finland, Norway, and Sweden ranging from 41.3% to 64.4% respectively.

The two main reasons that led to the high mortality rates according to a later announcement of ECDC were a) people not promptly taking the proper antiviral medicine when the first indication of serious clinical symptoms appeared and b) people not promptly being admitted into intensive care units in hospitals. (HCDCP, 2013).

Another evident fact is that patients with an infection from the virus A(H1N1)pdm09 remained hospitalised longer than those infected by the ordinary seasonal flu (Rovina et al., 2014). Therefore, by detecting the areas that were greatly affected by the virus, authorities would be able to prepare and expect that hospitals would be receiving a large surge of patients. Our study indicates the regions that were greatly influenced by the virus A(H1N1)pdm09. It is eminent that during the past years, even though great efforts have been made to create state-of-the-art health centres in the peripheral areas, the more central areas continue to be superior not only in quality but quantity as well, as not all areas have tertiary care (Petrakos and Psycharis, 2016). The authorities ought to in case of a new pandemic wave be able to distribute proportionally and equally the vaccines throughout the country (Tsoucalas and Sgantzos, 2016; Giannouli, 2010) and rectify inaccuracies made during the pandemic A(H1N1)pdm09 of 2009 by aiming to inform more accurately the general public, and especially those at high risk, of the vaccines.

The study and understanding of the phenomenon in Greece allow us to focus more cautiously in the next step for geographical areas that need a better allocation of resources, medical supplies and vaccination policy during a new epidemic or pandemic. The latter is possible with an integrated monitoring system of the evolution of the phenomenon using the current methodology of SMR’s and the corresponding mapping (in coordination with the Ministry of Health, the Ministry of Education and the HCDCP). It is worth mentioning that according to reports from schools of excess absenteeism (school’s student body), the phenomenon peaked two weeks earlier (46th and 47th) in young children and especially primary Schools from what HCDC (48th) declared in the general population (Doukissas et al., 2016).

Concluding, preventive measures, especially in the youth population, should be taken into consideration since at present mortality continues at very high levels in Greece. According to more recent HCDCP data due to deaths from influenza A(H1N1)pdm09 received by the authors after a formal request, during the period 2013 - 2014 there is a rapid increase of deaths (107). It is worth noting that mortality remains particularly high in the years 2015 - 2016 where 156 deaths occurred. The recent financial crisis in Greece has aggravated the situation (lower public spending and private incomes led to the decline of medical care). Therefore, governmental actions are crucial in controlling the effects of the flu every year. The regions affected the most, i.e. Thessaly, Southern Aegean Islands and Central Macedonia should be pioneers in this effort. Our findings may help stakeholders to consider a more efficient policy in a probable future flu epidemic. Such an example could be a more efficient distribution and better organisation of intensive care units or hospital beds in each of the thirteen Greek regions.

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