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STUDY OF INFLUENZA RELATED MORBIDITY

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Resumen

La morbilidad relacionada con la gripe puede verse reflejada en distintos grados desde una consulta al médico de cabecera sobre el uso de medicamento hasta el ingreso hospitalario. En el presente estudio se estudia la relación entre dos distintas fuentes de casos de influenza con distinto grado de severidad según las Comunidades Autónomas de España. Los resultados del modelo indicaron que el modelo *Zeroinflated* era el mejor ajuste para describir la relación entre ambas fuentes de datos. La relación exponencial muestra cómo los ingresos hospitalarios de influenza aumentan con un cierto retardo en comparación con las enfermedades de declaración obligatoria de influenza. Se requieren significativamente más casos de influenza en las declaraciones obligatorias para provocar un aumento en los ingresos hospitalarios. Además, los resultados indican una alta variabilidad de la tasa de crecimiento exponencial entre las distintas regiones de España.

Palabras claves: morbilidad, influenza, España, modelo, ingreso hospitalario, enfermedades de notificación obligatoria

Abstract

Influenza related morbidity can be reflected in varying degrees from a physician's visit, to a hospital admission, to the use of medication. In the present investigation, the relationship between two different sources of influenza cases with different degrees of severity according to the Autonomous Communities of Spain were examined. The model results indicated that the Zeroinflated Model was the best fit for describing the relationship between both data sources. The exponential relationship shows how the influenza hospital admissions increase with a delay effect in comparison to influenza notifiable diseases. Significantly more notifiable diseases are necessary to cause an increase in the hospital admissions. In addition, the results indicate a high variability of exponential growth rate between the several regions in Spain.

Keywords: morbidity, influenza, Spain, modelling, hospital admissions, notifiable diseases

1. Introduction

Global change is undoubtedly one of the most important issues that humanity must face in the XXI century. It is characterized by multiple dimensions (physical, environmental, social, political, economic and demographic) and is considered to be an interdisciplinary topic. Climate change – as an extreme expression of atmospheric variability – is increasingly showing the vulnerability of modern societies to new environmental scenarios. The welfare of each individual is inextricably linked to global health. This statement is even more important when talking about public health and infectious diseases. The nature and intensity of environmental impacts on human health do not homogenously affect all spatiotemporal scales. The availability of large amounts of data, which directly or indirectly reflects the people´s health conditions, is becoming an extraordinary source of knowledge in the information society.

The concept of global health implies the need to combine and connect health data with different sources (environmental, social, networks, etc.) in order to provide added value to the available raw data. It is through this added value of digital data where new answers to current problems can be found. There are uncountable sources of datasets of physical and social elements. The integration and combination of these huge heterogeneous variables is a major challenge (Fdz.de Arroyabe & Royé 2017). One of the most recurrent global infectious diseases is influenza. Europe has undergone major influenza epidemics throughout history (Potter 2001, Baltazar Nunes et al. 2011). Effective management of this disease requires the availability of data with high spatiotemporal resolutions.

It is undeniable that the environment directly and indirectly influences the state of human health. The human body and the atmosphere are in a physical and chemical equilibrium of constant exchange. All human beings are forced to react to the atmospheric elements to ensure correct and optimal organ function. Environmental effects on human health have different responses in the sense of an Illness-Wellness Continuum (Gavidia & Talavera 2012).

Mortality is, on the one hand, a premature consequence, and on the other, affects a smaller part of the population than the possible effects in morbidity (Laschewski & Jendritzky 2002). The circumstances associated with morbidity can be very diverse (Fig. 1). Depending on the seriousness of the response, more or less of the population is affected. Obviously, many of the impacts of atmospheric changes on human health do not end with death or with a hospital admission. A large part can be manifested through a visit to the doctor or self-medication.

However, data is not available for all levels of morbidity due to the simple fact that they are not considered relevant by the administration. Furthermore, deficiencies in accuracy, viability and completeness in a spatial-temporal sense can lead to problems when working with certain data sources. In this study, two of the main sources of influenza records in Spain, Notifiable Diseases (ND) and hospital admissions (HA), were compared with the aim of identifying the shape of the relationship and its appropriateness for conducting public health studies. Notifiable disease surveillance systems are essential for infectious disease prevention at multiple scales from local to global.

In the case of Notifiable Diseases, the main deficiency lack of completeness (Silk and Berkelman 2005). ND as epidemiological surveillance include, amongst others, Influenza, Legionellosis, HIV, Hepatitis A/B/C or Tuberculosis. One problem with the specific case of influenza is that the cases are mostly suspected rather than confirmed by a laboratory test. In addition, the temporal reference for flu cases is the epidemiological week, which does not coincide with that for environmental changes, which are recorded daily (mainly) or subdaily. In order to study health impacts caused by environmental factors, the temporal resolution is an essential element. In this regard, HA have a much better temporal resolution than ND. In summary, it would be important to record ND also on a daily basis as weekly resolution is a problem in these kinds of ecological approaches. In addition, primary care physicians participate in infectious disease surveillance through mandatory reporting. Thus, general practitioners have a key role in the notification of these kinds of diseases. This is an important point in relation to the total number of influenza cases that are recorded. Even though notification of influenza cases is compulsory, it ultimately depends on physicians' willingness to inform the competent agency at the regional or national level.

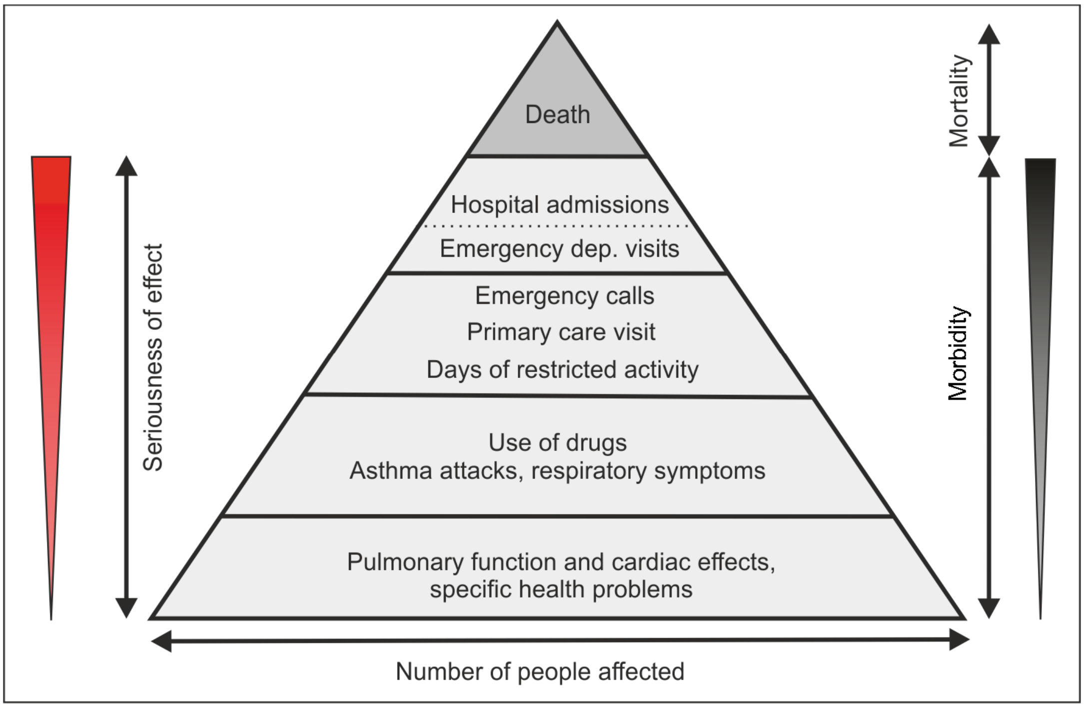


Figure 1 – Environmental effects on cardio-respiratory diseases. Source Modified according to EEA (2013)

Figure 2 – Participation in Notifiable Diseases by sanitary areas in Galicia, Spain, between 1991 and 2011.

Figure 2 shows the spatial and temporal variability of participation in notification of the influenza cases in different sanitary areas of the Autonomous Community of Galicia. Furthermore, the two data sources considered in this study represent different degrees of seriousness. Influenza related hospital admissions mainly affect the elderly with chronic diseases or substantial health problems. On the other hand, the cases reported by general practitioners represent a lower level of medical care.

2. Methods

2.1- Data sources

First, information on influenza cases related to Notifiable Diseases (ND) has been provided for the period between the years 2003 and 2013 by the Spanish Surveillance System for Influenza at the National Center for Epidemiology in the Health Institute Carlos III. The main concern with this type of data record is related to it being considered as reporting on probable cases. In this sense, it has been demonstrated that medical doctors can identify influenza cases from other non-infectious diseases such as colds. There is a high statistical correlation between series of notifiable cases and isolated influenza cases in laboratory.

Secondly, the registers of Hospital Admissions (HA) due to influenza (International Classification of Diseases and Related Health Problems Version 10: J09-J10) were recorded by the Institute of Sanitary Information in the Spanish Ministry of Health, Social Services and Equality. Primary and secondary diagnoses have been delivered for the same time period. This registry does not represent the population's reality of respiratory disease morbidity but the registered demand for specialized care hospitalization services. Furthermore, the country's hospitals are not 100% covered, but the HA include 100% of the acute hospitals in the network of the National Health Services (public and publicly funded). Gradually, since 2005, private sector acute hospitals have also been incorporated into the network.

2.2- Statistical analysis

The relationship between the two data sources, influenza cases and hospital admissions, is studied using different statistical models for describing the existing correlation. In addition, an exploratory analysis of hospital admissions is performed, which is useful and possible due to the presence of multiple additional variables such as gender, age or severity in the data source. In all model fits, hospital admissions are the dependent variable and the influenza cases of Notifiable Diseases are included as the independent one.

For the statistical analysis, the time series of HA and ND were arranged by Autonomous Communities (except for Ceuta and Melilla Autonomous Cities) and the HA aggregated weekly to make them comparable. The following models were fitted: Linear Model (LM), Generalized Linear Model (GLM) (McCullagh and Nelder 1989), Generalized Additive Model (GAM) (Hastie and Tibshirani 1990, Wood 2006) and a Zeroinflated Model (Zeroinf) (Cameron and Trivedi 2005). In the two first models the {stats} package of the R environment were used. In the case of the GLM, a Poisson distribution was selected. Moreover, the GAM was fitted with the {mgcv} package, version 1.8-15, and the Zeroinf with the {pscl} package, version 1.4.9. In both models the selected distribution is negative binomial. All models, statistical analysis and graphic results were performed with the free software environment R, version 3.3.

3. Results and Discussion

In Figure 3, the time series of hospital admissions and notifiable diseases due to influenza are shown for Spain between 2003 and 2013. A low number of hospital admissions from 2003 to 2009 and a sudden increase in the total number starting in 2010 can be observed. This is a peculiar pattern which is highlighted in comparison to influenza cases of ND showing a more seasonal pattern over time. There is only a clear anomaly in 2005, and higher values than normal in three of the last four years of the study period.

A satisfactory explanation for the low number of hospitalizations from 2003 to 2009 in comparison to the later years is not possible at this moment, but the increase in the mean age of the patient and greater or lesser severity of epidemics could be the cause. However, both time series reflect the well-known seasonal behavior of influenza, with a high interannual variability. In addition, the absolute magnitude is considerably higher in the observed cases of Notifiable Diseases than in Hospital Admissions. This is related to a higher degree of affected population and a less degree of seriousness in the case of Notifiable Diseases. The Pearson correlation coefficient between both influenza data sources is significant with R 0.52 (p < 0.001). It should be noted that the proportion of hospital admissions with influenza as principal diagnosis is 60.8% of all observed cases in Spain. 24.4% correspond to persons older than 64 years of age, and 23% to children five years old or less.

In Figure 4 the distribution of the hospital admission rate per 1000 inhabitants according to age and gender (a) and severity (b) is visualized. First, it can be seen that the vulnerable groups are children under 5 years, with a rate of 17 per thousand, and the elderly over 65 years, with a rate of 3 to 6 per thousand. The high rate of hospital admission for children is likely related to greater precautions by the medical staff which is confirmed when comparing the severity and the same age range in Figure 4b. Furthermore, gender differences are clearly highlighted over the age of 70. The differences could be explained by various factors. For example, there is a clear heterogeneous distribution of chronic problems between the two genders (Case et al. 2005). In this context, one must bear in mind the influence of social determinants, especially lifestyle, which could account for these differences. Case et al. (2005) indicate more specific behavior in certain health conditions in which men tend to be hospitalized and to die with higher probability than women with the same conditions. In Figure 4b, the higher severity in the elderly and the high admission rate of children with low severity is clearly marked.

The model results indicated that the Zeroinflated Model was the best fit for describing the relationship between both data sources, which is confirmed by the analysis of variance (Figure 5). Since the time series contains many zeros, and in consequence is inflated, it is a reasonable outcome. The shape corresponds to positive exponential behavior between both influenza data sources. The exponential relationship shows how the hospital admissions increase with a delay effect in comparison to ND cases. Significantly, more ND cases are necessary to cause an increase in hospital admissions. This is mainly related to the characteristics of hospital admissions itself, since hospital admissions represent the patients with the most severe cases. Also. shape changes between different seasons could be ascertained, different degrees of exponential growth, which reflect the degree of severity influenced by environmental factors (temperature, humidity) or influenza subtypes (Hui and Hayden 2014, Towers et al. 2013, Tsuchihashi et al. 2011). Likewise, the relationship must be understood considering the criteria used to classify the records from the hospital admissions. Any patient with influenza code in the primary or secondary diagnosis was selected. This indicates that influenza was not always the main reason for admission to the hospital.

For the comparison between different Spanish autonomous communities, the fitted model data were normalized (Figure 6). The results indicate a high variability of exponential growth rates between the several regions in Spain. For example, Madrid and Cataluña show a later exponential development of hospital admissions compared with Andalusia and Islas Baleares where the relationship is characterized by a significantly smaller degree of exponential growth. It is therefore important to find out the spatial variability of this relationship between the two sources bearing in mind social, administrative and geophysical aspects. According to Merler and Ajelli (2010), how population heterogeneity and different patterns of human mobility affect the course of influenza in terms of timing and impact is still insufficiently known.

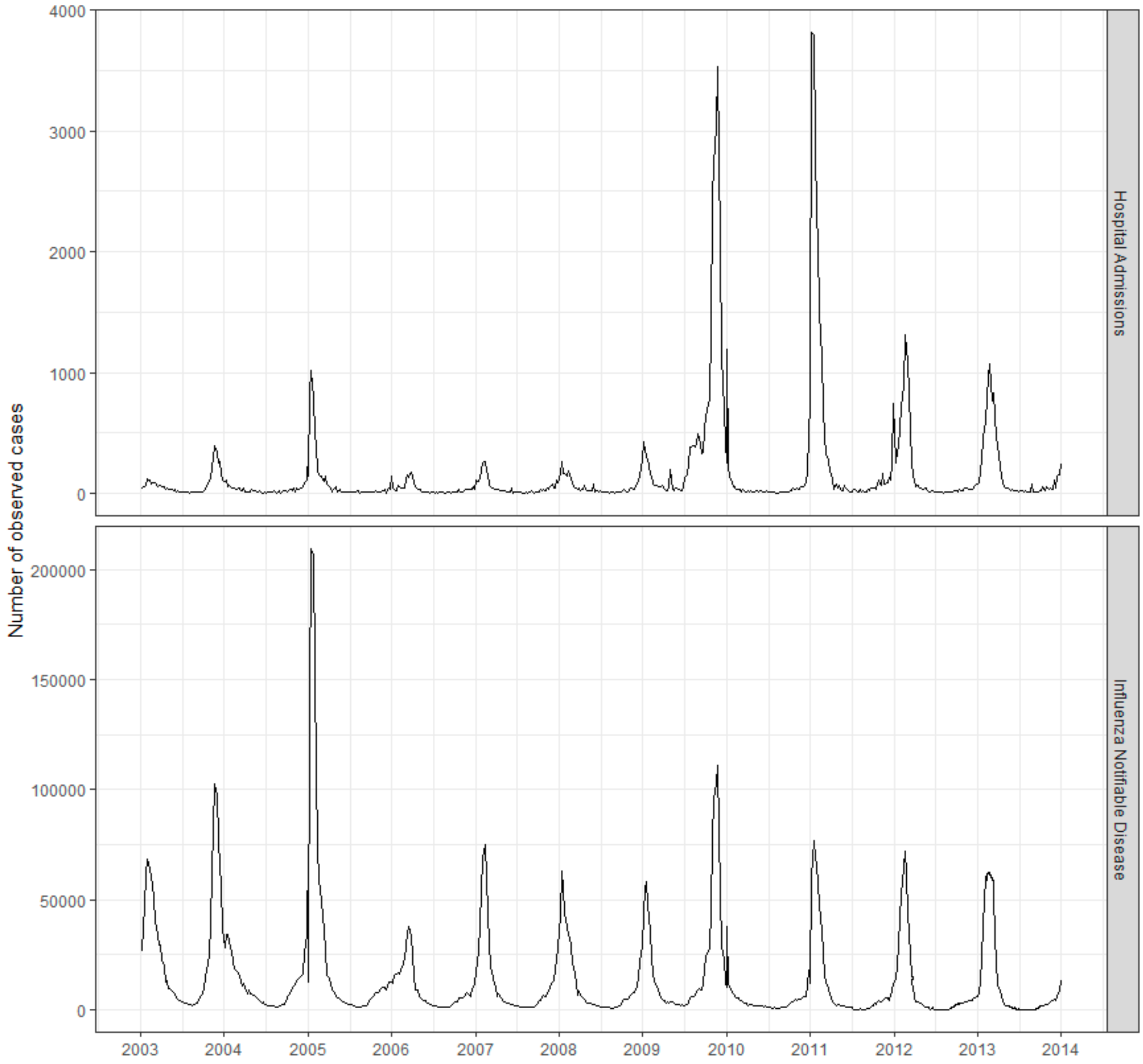
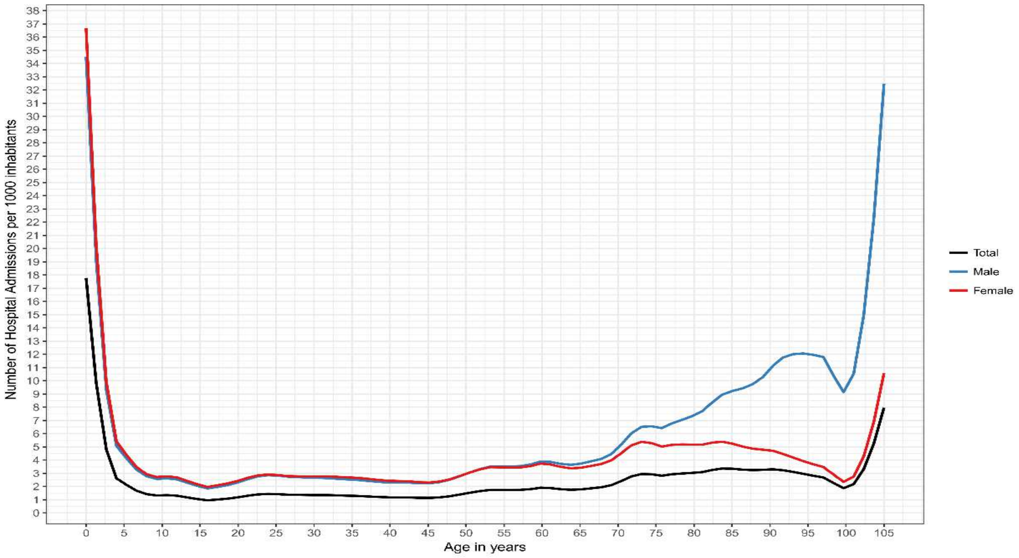


Figure 3 – Hospital admissions and notifable diseases due to influenza between 2003 and 2013 in Spain.

The different degrees of exponential growth can be a result of multiple causes, such as the presence of a specific virus type, socioeconomic or demographic characteristics, an important social event or certain climatic conditions in an area. Advances in understanding and management of infectious diseases such as influenza will necessitate the ability to develop technical tools and new scientific knowledge based on the use of these large amounts of heterogeneous datasets.

a)



b)

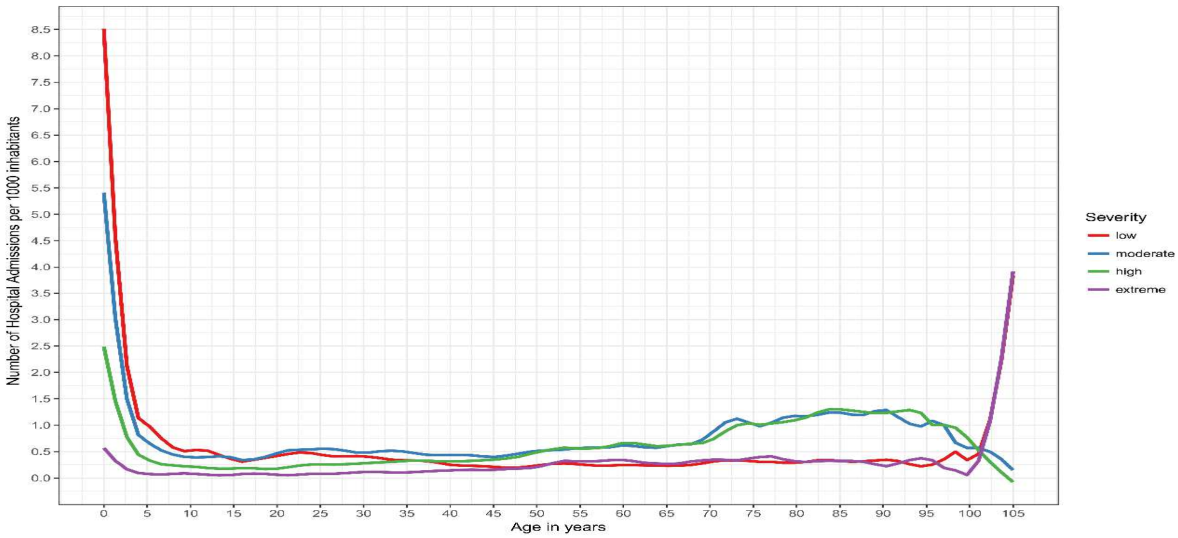


Figure 4 – Distribution of the hospital admission rate per 1000 inhabitants according to age and gender (a) and severity (b) (population reference is the census 2011 INE).

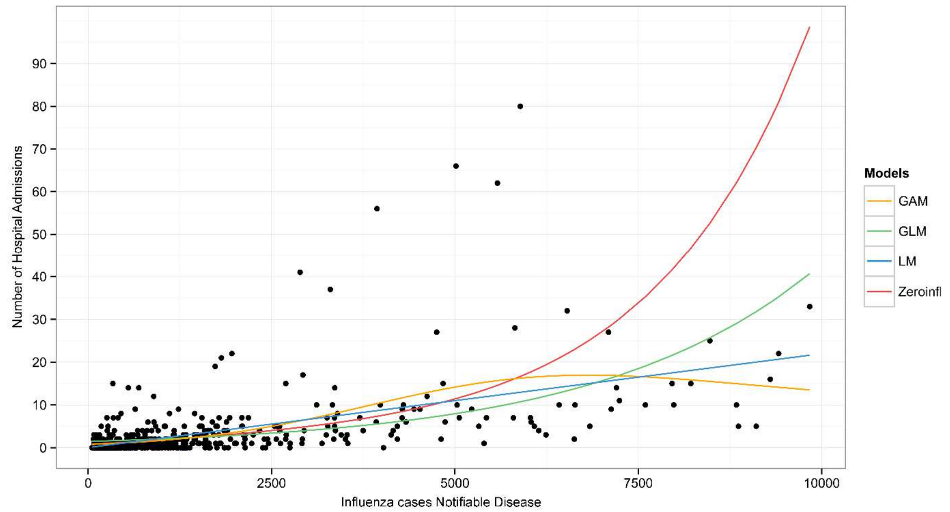


Figure 5 – Example of Relationship between hospital admissions and Influenza cases with multiple model fits for the Galician autonomous community.

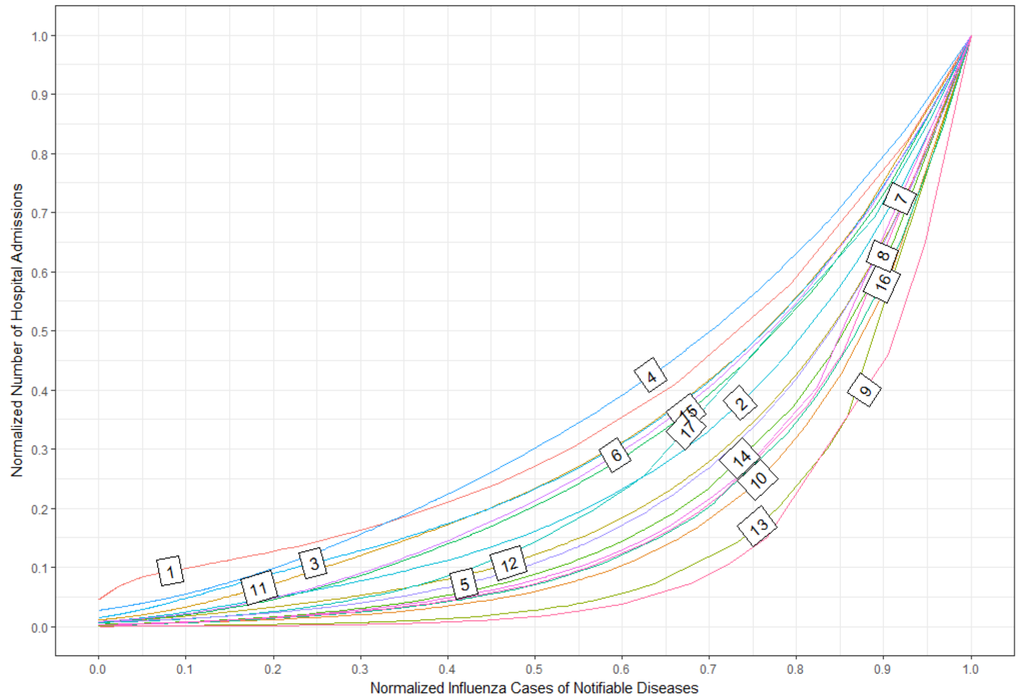


Figure 6 – Normalized relationship between Hospital Admissions and influenza cases for each autonomous community according to the Zeroinflated models (1:Andalucia, 2:Aragón, 3:Asturias, 4:Baleares, 5:Canarias, 6:Cantabria, 7:Castilla-La Mancha, 8:Castilla y León, 9:Cataluña, 10:Comunidad Valenciana, 11:Extremadura, 12:Galicia, 13:Madrid, 14:Murcia, 15:Navarra, 16:País Vasco, 17:Rioja

4. Conclusions

It is important to point out the relevance of influenza as an infectious disease which has many social and economic implications in society. The significance of this disease in relation to public health activity during the epidemic season is a global concern in relation to morbidity and mortality in many societies around the world, especially for those that are demographically characterized by elderly groups.

The main result of this study is the presence of an exponential growth between influenza notifiable diseases and hospital admissions which is statistically noteworthy. The complexity of working with heterogeneous information (meteorological datasets, medical records, social and individual parameters) and different temporal and spatial resolutions introduce important uncertainties in the results that has to be carefully analyzed in the future.

Despite the severity in the case of hospital admissions, the use of this data source has several advantages on the basis of the daily temporal scale, the available variables (age, sex, diagnosis), spatial resolution, viability, etc.

In this sense, the different degrees of exponential growth registered by the Autonomous Communities are a result of multiple factors such as the virus types and their virulence, the seasonality of temperate climates, the atmospheric anomalies due to natural and forced variability and the wide spectrum of peoples' vulnerability linked to individual factors such as their age, gender, lifestyle and genetic background. The spatial dimensions of the problem also incorporates uncertainties to this complexity but at the same time, it gives enormous value to the biometeorological approach to the problem considering that spatial variability is mainly due to atmospheric, ecological and biophysical parameters.

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