The age-specific impact of influenza on hospital admissions and mortality in five countries in Europe

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Preface:
This report is the result of a fruitful collaboration between researchers from five European counries, all involved in research on influenza and its impact. This collaboration was enabled by an unrestricted grant of Sanofi Pasteur and Sanofi Pasteur MSD based in Lyon (France).
We thank the sponsors for enabling this important research. We express the hope that the results of this study will contribute to reduce the impact of seasonal influenza on hospitalizations and mortality in Europe.

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Executive Summary

Influenza has an important public health impact each winter in terms of illness, hospitalizations, mortality and socio-economic effects (e.g. work absences). To reduce this burden, vaccination programmes have been implemented across Europe since the 1980s/1990s.

In most countries, the vaccination programmes are targeted at the so-called high risk groups, meaning high risk for complications following influenza virus infection (e.g. persons aged ≥65 and persons with heart diseases and diabetes).

This report assesses the impact of seasonal influenza on hospitalizations and mortality in five European countries: England, France, the Netherlands, Portugal and Spain. It pays special attention to those aged 50-64, but also to children (aged 0-14) and those aged 65+.

A novel methodology was developed to assess both excess hospitalisations and mortality in each country. The methodology uses a Poisson regression model with the age specific ILI/ARI consultation rate as the independent variable. Virological data was used to define the period of influenza activity when excess hospitalisations or mortality was calculated.

A major advantage of a multi-country analysis is that exactly the same methodology is used to assess the excess burden of disease by age group. In the published literature different methodologies and datasets are used to estimate excesses and this makes it very difficult to compare national stimates.

The five country study found a high degree of consistency in the percentage of hospitalisations and mortality that could be attributed to influenza (e.g. 1.7-3.4% of all-cause mortality can be attributed to influenza in persons aged 50-64). It usually found that the excess burden was higher in the age group 65+ and lowest in children. Very similar results were found when the analysis was repeated for the number of excess deaths/hospitalisations per 100,000 population.

Our study found that part of the excess in hospitalisations and mortality seen in the five countries each winter can be explained by influenza but other factors (e.g. temperature, other respiratory viruses) probably also play an important role.

1 Introduction

Seasonal influenza epidemics are an important burden to public health across Europe [1, 2]. Infections caused by the influenza virus are not only responsible in terms of morbidity and mortality, but they also have an economic impact e.g. due to work absence and the use of health services. Therefore, vaccination of high risk populations and persons over 65 years has been implemented in Europe since the 1980/1990s [3-5].

With minor exceptions, vaccination recommendations are broadly similar across Europe, with most countries recommending the vaccination of persons over 65 years and high risk groups. The age threshold is 60 years in Germany, Hungary, and the Netherlands, and in Finland vaccination of children aged 6 months to 2 years has been recommended since 2007. In Austria vaccination is recommended for persons of all ages [6].

In several countries outside Europe, including the United States, vaccination recommendations have been changed to adults over 50 years old [7]. To make decisions about lowering the age for vaccination in Europe, it is important to study the impact of influenza on morbidity and mortality in different age groups.

Recently, a first attempt was made to estimate the age specific impact of influenza consultations due to influenza-like illness (ILI). In this study the excess of physician consultation rates for ILI was calculated in different age groups during influenza seasons in the Netherlands, England and Spain in the period 1994-2007 [8]. In Spain and the Netherlands a disproportionately higher burden of disease was found for the age groups <1, 1-4 and 5-14 years. There was no such evidence for the age group 45-64 years.

The influenza virus not only affects the number of contacts with GPs, but also affects mortality [3, 9, 10] and hospitalization rates [4, 11, 12] during influenza seasons. However, European studies on this subject are scarce and the available data are difficult to compare because different statistical methods are used. Therefore, in the present study age-specific impact of seasonal influenza epidemics on hospital admissions and deaths is studied in five European countries: the Netherlands, France, England, Portugal and Spain. An important advantage of the current study is that it is a multi-country study and uses the same methodology. This should allow more comparative estimates. The principle age group that was studied was adults aged 50-64, but for comparative reasons, data is also presented for children (0-14) and adults aged 65+.

2 Research questions

1. What is the impact of seasonal influenza epidemics on the number of hospital admissions for influenza related reasons and to what extent do hospital admission rates vary by age, by season and by country?

2. What is the impact of seasonal influenza epidemics on the number of deaths due to an influenza related cause and to what extent do mortality rates vary by age, by season and by country?

3 Methods

In this study we investigated the age-specific impact of influenza on mortality and hospital admissions in five European countries (the Netherlands, France, England, Portugal and Spain) in ten influenza seasons in the period 1996-2006. Per country, the weekly number of hospital admissions / number of deaths were used for the age groups 0-14 years, 50-64 years and 65 years and older. Age-specific consultation rates for influenza-like illness (ILI) and acute respiratory infections (ARI) at sentinel practices (ILI or ARI per 100,000 population) and virological data (all-age) were used as an indicator for influenza activity. In the following paragraphs the used datasets are described per country. The ICD codes used in this study are listed in Annex 3. The available data sets are also summarized in table 3.1.

3.1 Data sources

The Netherlands

Mortality data. Data about deaths were derived from the official death statistics held by Statistics Netherlands. Data include cause of death (ICD-9 coded), date of death, age and sex.

Hospital admissions. Hospital admissions were available from the "Landelijke Medische Registratie" (LMR). This database covers approximately 98% of all hospitals in the Netherlands and included data about date of discharge, diagnosis at discharge (ICD-9 coded), age and sex.

ILI-data. ILI data were collected in the 'Continuous Morbidity Registration Sentinel Stations The Netherlands', which is in operation since 1970 [4]. Throughout the year the sentinel general practitioners report weekly on various health items, including ILI. The network consists of approximately 65 GPs, their practice populations cover about 1% of the Dutch population and are nationally representative by age, gender, geographical distribution and population density. The case definition for influenza includes the presence of the following criteria: acute onset of disease, accompanied by a raised rectal temperature of >38°C and at least one of the following symptoms: cough, coryza, sore throat, frontal headache, retrosternal pain or myalgia.

Virological data. During each winter (weeks 40-20), sentinel GPs (are asked to) take samples from the nose and throat of randomly selected patients with ILI for virological determination, at least 2 patients per week, irrespective of severity of symptoms. If they do not encounter patients with ILI they are asked to swab ARI patients.

Available data. Available data for the Netherlands are described in table 3.1. Mortality data, ILI data and virological data were available for the period 1996-2006. Hospital admissions could only be calculated for the period 1996-2005, since the LMR had only a coverage of approximately 85% of the hospitals in 2006. It was not possible to use the age category 0-14 years in the Netherlands due to low numbers. Therefore, the age category 0-19 years was used instead. For 2006, all cause mortality could not be

calculated for the age category 0-19, because data from this age category were not available when the statistical analyses started.

France

Mortality data. Mortality data were derived from the National Statistics Office. Weekly data were available by age and gender.

Hospital admissions. The number of hospital admissions was not available for France.

ARI-data. ARI-data were used from the national influenza surveillance network called Réseau des GROG (Groupes Régionaux d'Observation de la Grippe/Régional groups for influenza surveillance) [13]. It includes approximately 600 sentinel physicians, 500 GPs (0.6% of French GPs) and 100 pediatricians (3.3% of French pediatricians). The GROG network uses a precise ARI definition: sudden onset of at least one respiratory symptom and at least one constitutional symptom in a context of acute infectious disease.

Virological data. From week 40-15 sentinel physicians are requested to take swabs from nose and throat to some of their ARI patients (alert period). During the epidemic, practitioners have to follow a swabbing protocol leading to random sampling. All swabs are analyzed in the 2 French National Reference Centres for influenza or 8 hospital virological labs. On average the network yields about 150 samples per week for virological determination.

Available data. Available data for France are described in table 3.1. Mortality data, ARI data and virological data were available for the period 2001-2006. It was not possible to use cause specific mortality data and therefore only all cause mortality is used in the statistical analyses.

England

Mortality data. Data were used from the Mortality Statistics of the National Statistics Online (ONS). Monthly data were available by diagnoses (ICD-9 coded), age and gender.

Hospital admissions. For the number of hospital admissions, the Hospital Episode Statistics (HES) was used. It included weekly numbers of hospital admissions by diagnosis (ICD-9 coded), age and sex.

ILI-data. ILI-data were used from The Royal College of General Practitioners Weekly Returns Service (WRS). It includes approximately 500 GPs covering 1.8% of the entire population, representative for age, sex socio-economic status and ethnic origin [14]. The WRS network has provided guidance on the use of the diagnosis 'ILI', though it is not considered an absolute definition. The guidance incorporates sudden onset of disease, fever or feverishness, at least one respiratory symptom and the presence of constitutional symptoms such as headache and muscle pains.

Virological data. From week 40-20 network GPs take swabs from the nose and throat of randomly selected patients with ILI; on average the network yields about 90 samples per week for virological determination.

Available data. Available data for England are described in table 3.1. Mortality data, hospital admissions, ILI data and virological data were available for the period 1997-2006. Only monthly mortality data could be used (instead of weekly data). For the analyses, the monthly data were evenly distributed over the weeks of the specific month.

Table 3.1: Datasets from the participating countries

		1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
The Netherlands	Mortality											
	Hospitalization											
	ILI-data											
	Influenza period (weeks)		1-7	4-14	52-9	50-4	52-8	5-13	9-15	49-1	4-10	6-12
France	Mortality											
	Hospitalization											
	ARI-data											
	Influenza period (weeks)							52-6	4-10	46-50	1-9	1-9
England	Mortality											
	Hospitalization											
	ILI-data											
	Influenza period (weeks)			3-13	52-8	48-2	3-9	51-3	2-12	43-49	52-11	1-9
Portugal	Mortality											
	Hospitalization											
	ILI-data											
	Influenza period (weeks)				51-5	1-7	50-9	2-6	46-4	45-49	1-5	
Spain	Mortality											
	Hospitalization											
	ILI-data											
	Influenza period (weeks)			2-6	2-10	51-5	3-13	1-7	4-18	44-50	51-4	

Portugal

Mortality data. Mortality data were derived from the official death statistics held by Instituto Nacional de Estatística. Data include cause of death (coded as ICD-9, 1996 to 2001, and ICD 10, from 2002 to 2004) date of death, age and sex.

Hospital admissions. Hospital admission data only regard public hospitals. The information was derived from "GDH: Grupos de Diagnósticos Homogéneos-Instituto de Gestão Informática e Financeira" database, that covers approximately 82% of all hospitals in the Portugal and includes data about date of admission, date of discharge, diagnosis at discharge (coded as ICD-9-CM), age and sex.

ILI-data. ILI data were collected in "Médicos-Sentinela"(MS) the Portuguese GP sentinel system that operates since 1991 [15]. This network is constituted by approximately 150 GP that participate voluntary way. The MS population under observation covers 1.2% of the Portuguese population and is representative by sex and age. During the study period the criteria for the incidence rate estimates has been based on the presence of 6 or more symptoms between the next set of symptoms (ICHPPC-2) : sudden onset, cough, chills, fever, weakness or exhaustion, body aches, sore throat with no relevant inflammatory signals and contact with patient with flu.

Virological surveillance. From week 40-20 network GPs are asked to take swabs from the nose and throat of all patients with ILI; on average the network yields about 10 samples per week for virological determination.

Available data. Available data for Portugal are described in table 3.1. ILI-data and virological data were available for the period 1998-2005, mortality data for the period 1998-2004 and hospital admissions for 2000-2005.

Spain

Mortality data. Data about deaths were derived from the official death statistics held by Instituto Nacional de Estadística (INE). Data included cause of death (coded as ICD-10), date of death, age and sex.

Hospital admissions. Hospital admission data were derived from the "Conjunto Mínimo Basico de datos (CMBD)". This database covers approximately 85% of all hospitals in Spain and includes data about date of discharge, diagnosis at discharge (coded as ICD-9-CM), age and sex.

ILI-data. The Spanish Influenza Sentinel Surveillance System (SISSS) was started in 1991 and consists of 497 GPs and 171 paediatricians who report weekly on ILI from week 40-20. SISSS includes 16 regions together covering 2% of the Spanish population. The network is representative for sex, age and level of urbanisation [16]. Spain uses the case definition provided by the International Classification of Health Problems in Primary Care (ICHPPC) [17]. This is based on either positive culture of influenza virus or serological evidence of influenza infection; or includes, in the presence of influenza activity, 4 of the following characteristics: 1) sudden onset (within 12 hours), 2) cough, 3) fever or chills, 4) prostration, weakness, myalgia or general pain, 5) rhinitis, pharyngitis, contact with a case.

Virological data. From week 40-20 sentinel physicians are requested to take swabs from nose and throat of randomly selected patients with ILI for virological determination, on average resulting in about 35 specimens per week for virological determination.

Available data. Available data for Spain are described in table 3.1. Mortality data,

hospital admissions, ILI data and virological data were available for the period 1997-2005. Only hospital admissions due to the diagnosis 'Pneumonia and Influenza' could be used for statistical analyses.

3.2 Statistical analyses

Per country, if available, five variables were used as dependent variables: 1) all cause mortality per week, 2) mortality due to respiratory diseases per week, 3) mortality due to pneumonia and influenza per week, 4) number of hospitalizations due to respiratory diseases per week and 5) number of hospitalizations due to pneumonia and influenza per week. For the five dependent variables, models were calculated for the populations 0-14 years (0-19 years for the Netherlands), 50-64 years and 65 years and older. For the age category 0-14 years old, mortality due to respiratory diseases and mortality due to pneumonia and influenza were not used as dependent variable due to low numbers.

The age-specific consultation rates for influenza-like illness (ILI) and acute respiratory infections (ARI) at sentinel practices were used as the indicator for influenza activity. The excess mortality or hospitalisations due to influenza is the difference between the model without adjustment for influenza activity and the model with adjustment for influenza activity. In the tables in Annex 2, this is presented as the 'Predicted' number. It should be noted that by using this model there is automatically no excess mortality/ hospitalizations in weeks without influenza activity.

First, in the null-model the observed numbers per week were reconstructed in a multi-level Poisson model with a random intercept with Fourier series (series of sinuses and cosines (number of weeks/2 minus 1)), and a second order polynomial to correct for variation between seasons. Fourier series were estimated by country and the course of the dependent variable was allowed to vary between different influenza seasons. In graph 3.1A and 3.1B the observed numbers and calculated numbers by the model are plotted for the Netherlands.

Second, the number of ILI / ARI contacts was added to the null model to predict the number of deaths/hospitalizations in a particular week caused by influenza. The number of ILI contacts was standardized (z-scores) for each country to make a comparison between different years within a country possible. The z-score in a particular week was calculated by the following formula:

z-score = (ILI rate – mean ILI rate)/standard deviation

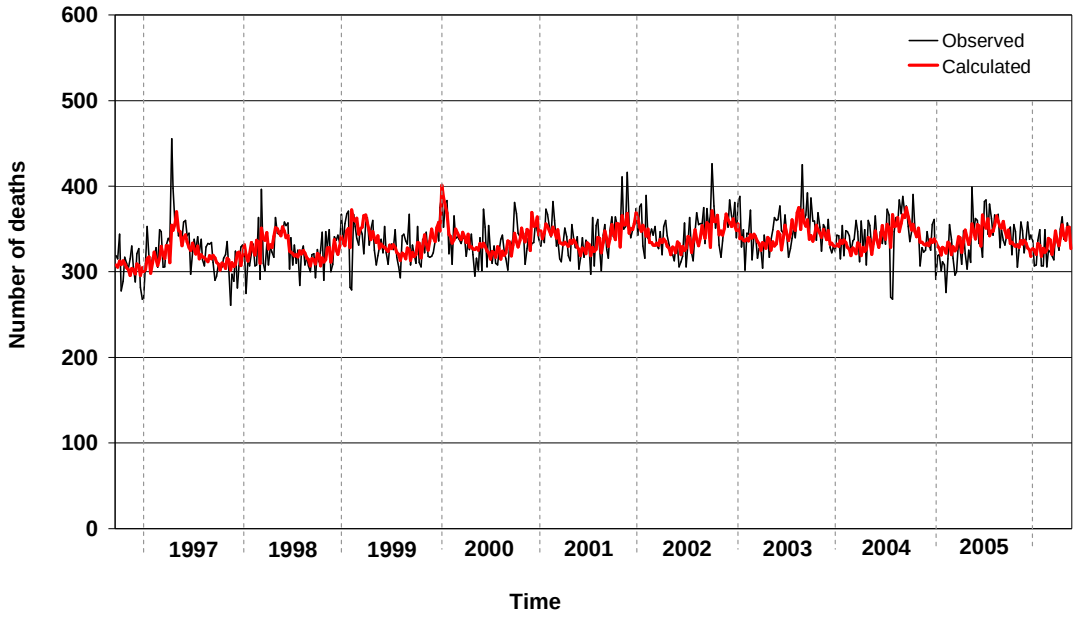
Only the positive z-scores were used in the statistical analyses; negative z-scores were counted as zero. In graph 1A-1E in annex 1, for all countries the influenza activity was plotted per age category.

Finally, in the virus active influenza weeks the observed number of deaths/ hospitalizations and the number of deaths/hospitalizations caused by influenza were calculated per week and age category. The used method for defining the influenza active

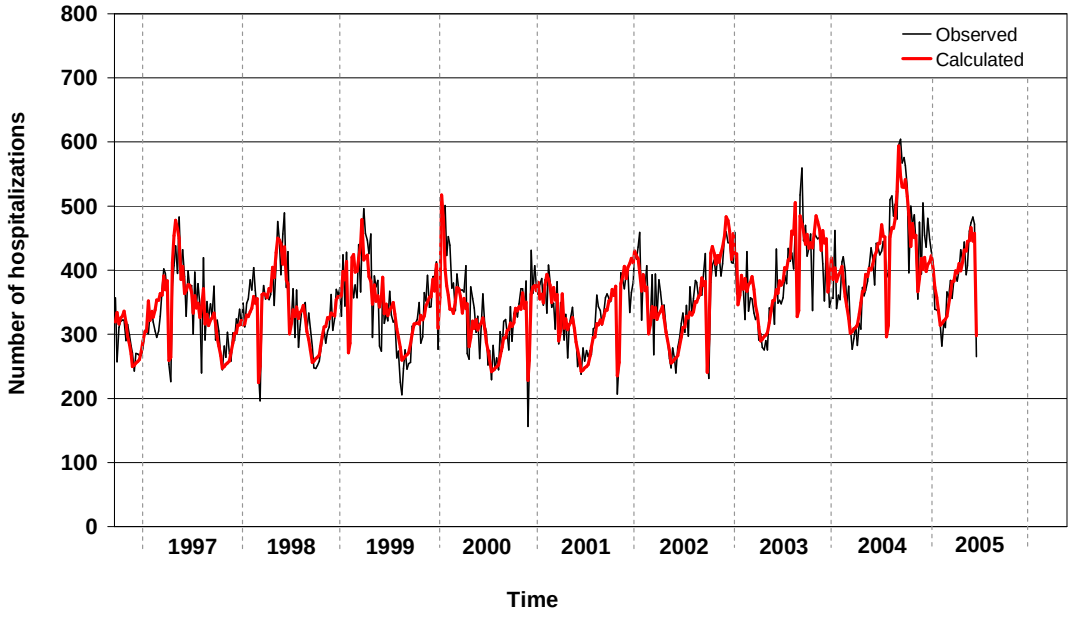
weeks is shown in graph 3.2. Peak weeks were defined as those weeks in which 70% of all influenza virus-positive samples are detected in a given influenza season. 95% confidence intervals were calculated around the totals.

Unfortunately, RSV detections were not included in the final model as we were unable to obtain this data for all five countries.

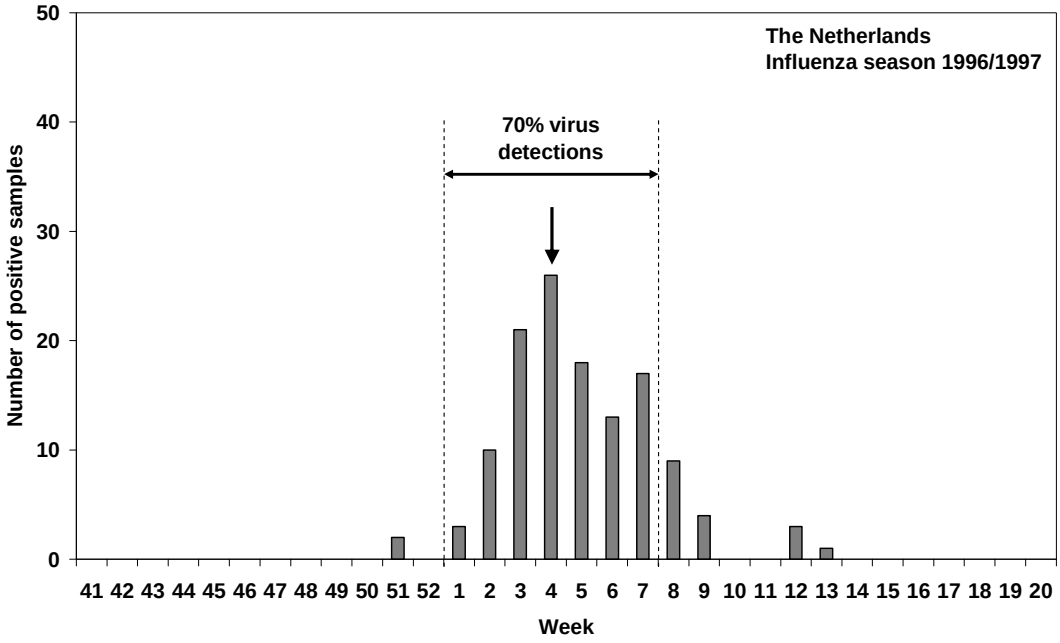
Graph 3.1A: The observed number of total deaths per week and the number of deaths calculated by the model in the age group 50-64 years in the Netherlands.



Graph 3.1B: The observed number of hospitalizations due to respiratory diseases per week and the number of hospitalizations calculated by the model in the age group 50-64 years in the Netherlands.



Graph 3.2: Method for defining the influenza period.



4 Results

4.1 Observed number of deaths and hospitalizations over time

In this section the observed number of deaths and hospitalizations over time are described per country. The graphs A2-A21 are shown in the annex 1.

The Netherlands
In the Netherlands, the highest all cause mortality rates were found for the age category 65 years and older with the highest peaks in the influenza seasons 1997/1998, 1999/2000 and 2003/2004 (peaks over 3000 deaths) (graph A2). In the age categories 0-19 years and 50-64 years the number of deaths stabilized over time around 35 and 335 deaths per week, respectively. For the mortality caused by respiratory diseases and pneumonia and influenza, the highest numbers were found in 1999/2000 for both diagnoses and age categories (graph A3 and A4).
Hospital admissions due to respiratory diseases (graph A5) were highest in the age category 0-19 years with the highest peaks in the period 1996-1999 (>2000 per week). On the other hand, hospital admissions due to pneumonia and influenza (graph A6) were highest for the age category 65 years and older with peaks in the period 2003-2005 (> 500 admissions/week).

France
For France, the highest all cause mortality rates were found for the age category 65 years and older with a peak in the summer of 2003 and the influenza season 2004/2005 (>10000 deaths). In the age categories 0-14 years and 50-64 years the number of deaths stabilized over time at around 90 and 1300 deaths per week, respectively (graph A7).

England
All cause mortality in England was the highest for the age category 65 years and older with peaks in the influenza seasons in the period 1998-2000 (>12,000 deaths/ week). In the age categories 0-14 years and 50-64 years the number of deaths stabilized over time around 85 and 1060 deaths per week, respectively (Graph A8). Mortality due to respiratory diseases and pneumonia and influenza was increased in the period 1998-2000 for the age group 65 years and older (Graph A9 and A10).
Hospital admissions caused by respiratory diseases pneumonia and influenza were highest in the age category 65 years and older (Graph A11 and A12). For both diagnoses, highest peaks were found in the influenza seasons 1998/1999 and 1999/2000 (>10,000 and 3,000 admissions per week, respectively).

Portugal
Highest all cause mortality rates in Portugal were found for the age category 65 years and older with the highest peaks in the influenza seasons in the period 1998-2000 (>2,500 deaths/week). In the age categories 0-14 years and 50-64 years the number of deaths stabilized over time at around 30 and 175 deaths per week, respectively (Graph A13). The

same trend was found for mortality caused by respiratory diseases and pneumonia and influenza (Graph A14 and A15).
Hospital admissions caused by respiratory diseases pneumonia and influenza were both highest in the age category 65 years (Graph A16 and A17) and older with the highest peaks in the influenza season 2004/2005 (>2,000 and >1,000 admissions per week, respectively).

Spain
All cause mortality in Spain was the highest for persons over 65 years older. Peak rates were found in the influenza season 2004/2005 (around 10,000 deaths/ week). In the age categories 0-14 years and 50-64 years the number of deaths stabilized over time around 55 and 750 deaths per week, respectively (Graph A18). The same trend was found for mortality caused by respiratory diseases and pneumonia and influenza (Graph A19 and A20).
The highest hospital admissions rates caused by pneumonia and influenza were found for the age category 65 years and older with the highest peaks in the influenza season 2004/2005 (>2,500 admissions per week; Graph A21).

4.2 The number of deaths caused by influenza

The number of deaths caused by influenza are described for all countries per influenza season in table A1-A13 in Annex 2. An overview of the results is presented in table 4.1. In the following paragraphs the results are described by country.

The Netherlands
The percentage of (all cause) deaths predicted by influenza was 0.3%, 2.5% and 5.5%, respectively for the age groups 0-19 years, 50-64 years and 65 years and older (table 4.1). The highest percentage was found in the age group 65 years and older in the influenza season 1999/2000 (14.3%; table A1).
The percentage deaths to respiratory diseases predicted by influenza activity (table A2) was 14.2% for age categories 50-64 years and 65 years and older. The percentage deaths to pneumonia and influenza predicted by influenza activity (table A3) was 18.1% for the age group 65 years and 16.4% for 50-64 years old.

France
The percentage of deaths predicted by influenza was 0.3%, 2.1% and 5.0%, respectively for the age groups 0-14 years, 50-64 years and 65 years and older (table 4.1). The highest percentage predicted deaths was found in the influenza season 2001/2002 in the category over 65 years old (6.9%; table A4).

England
The percentage deaths predicted by influenza was 0.3%, 1.7% and 3.2%, respectively for the age groups 0-14 years, 50-64 years and 65 years and older (table 4.1). The highest number of deaths predicted by influenza was found in the persons over 65 years in the influenza season 1999/2000 (13.5%; table A5).

The percentage deaths due to respiratory diseases predicted by influenza (table A6) for the age categories 50-64 years and 65 years and older was 9.4%. The percentage pneumonia and influenza deaths predicted by influenza (table A7) was 12.1% for persons over 65 years old and 11.8% in the group 50-64 years old.

Portugal

The percentage deaths predicted by influenza in Portugal was 0.3%, 2.1% and 4.7%, respectively for the age groups 0-14 years, 50-64 years and 65 years and older (table 4.1). The highest percentage was 11.6% in the season 1998/1999 in the age group 65 years and older.

The percentage deaths to respiratory diseases predicted by influenza activity (table A9) was 12.8% for persons over 65 years old and 11.8% for the age category 50-64 years. The percentage deaths due to pneumonia and influenza predicted by influenza activity (table A10) was 17.1% for the age group 65 years and older and 15.9% for the group 50-64 years old.

Spain

The percentage deaths predicted by influenza in Spain was 0.5%, 3.4% and 7.4%, respectively for the age groups 0-14 years, 50-64 years and 65 years and older (table 4.1). The highest percentage was found in the influenza season 1998/1999 in the persons over 65 years old (14.9%).

The percentage deaths due to respiratory diseases predicted by influenza (table A12) was 19.4% for the age category 50-64 years and 19.3% in persons over 65 years old. The percentage deaths to pneumonia and influenza predicted by influenza was around 25% (table 13).

Table 4.1: Overview of the percentage of deaths [95% confidence interval] predicted by influenza per country

	The Netherlands	France	England	Portugal	Spain
0-14 years*					
All causes	0.3% [0.1 – 0.6%]	0.3%[0.1 – 0.5%]	0.3% [0.1 – 0.4%]	0.3% [0.0 – 0.6%]	0.5% [0.2 – 0.7%]
50-64 years					
All causes	2.5% [2.3 – 2.6%]	2.1% [2.0 – 2.2%]	1.7% [1.6 – 1.8%]	2.1% [1.8 – 2.3%]	3.4% [3.2 – 3.5%]
Respiratory diseases	14.2% [12.4 – 15.9%]	---	9.4% [8.8 – 10.0%]	11.9% [9.4 – 13.4%]	19.4% [18.2 – 20.7%]
Pneumonia and influenza	16.5% [13.0 – 19.9%]	---	11.8% [10.7 – 12.9%]	16.1% [11.4 – 20.8%]	24.6% [21.4 – 27.8%]
65+ years					
All causes	5.5% [5.4 – 5.6%]	5.0% [4.9 – 5.1%]	3.2% [3.2 – 3.3%]	4.7% [4.6 – 4.9%]	7.4% [7.3 – 7.5%]
Respiratory diseases	14.2% [13.8 – 14.6%]	---	9.4% [9.3 – 9.6%]	12.8% [12.2 – 13.4%]	19.3% [19.0 – 19.6%]
Pneumonia and influenza	18.1% [17.5 – 18.8%]	---	12.1% [11.9 – 12.3%]	17.1% [16.1 – 18.1%]	25.1% [24.5 – 25.8%]

* 0-19 years for the Netherlands

Table 4.2: Overview of the percentage of hospitalizations [95% confidence interval] predicted by influenza per country

	The Netherlands	France	England	Portugal	Spain
0-14 years*					
Respiratory diseases	0.1% [0.1 – 0.2%]	---	0.0% [0.0 – 0.0%]	0.1% [0.1 – 0.1%]	---
Pneumonia and influenza	3.2% [2.8 – 3.5]	---	0.9% [0.8 – 1.1%]	2.6% [2.2 – 3.0%]	8.4% [8.1 – 8.8%]
50-64 years					
Respiratory diseases	4.3% [4.1 – 4.5%]	---	2.7% [2.6 – 2.8%]	4.8% [4.3 – 5.3%]	---
Pneumonia and influenza	5.6% [5.0 – 6.2%]	---	3.3% [3.1 – 3.6%]	5.9% [4.9 – 6.8%]	12.3% [11.8 – 12.8%]
65+ years					
Respiratory diseases	5.1% [4.9 – 5.2%]	---	3.8% [3.8 – 3.9%]	4.4% [4.2 – 4.6%]	---
Pneumonia and influenza	6.1% [5.8 – 6.5%]	---	4.3% [4.2 – 4.4%]	5.0% [4.7 – 5.3%]	10.9% [10.7 – 11.1%]

* 0-19 years for the Netherlands

4.3 The number of hospitalizations caused by influenza

The number of hospitalizations caused by influenza are described for all countries per influenza season in table A14-A20 in Annex 2. An overview of the results is presented in table 4.2. In the following paragraphs the results are described by country.

The Netherlands
The percentage hospitalisations due to respiratory diseases predicted by influenza activity was 0.1%, 4.3% and 5.1%, respectively for the age groups 0-19 years, 50-64 years and 65 years and older (table 4.2). The highest percentages were found in the influenza season 1999/2000 (table A14). The percentage hospitalisations due to pneumonia and influenza predicted by influenza varied between 3.2 and 6.1% (table 4.2).

England
The percentage hospitalisations due to respiratory diseases predicted by influenza activity in England was 0%, 2.7% and 3.8%, respectively for the age groups 0-14 years, 50-64 years and 65 years and older (table 4.2). In all age categories the highest percentages were found in the season 1999/2000 (table A16). The percentage hospitalisations due to pneumonia and influenza predicted by influenza varied between 0.9 and 4.3% (table 4.2).

Portugal
In Portugal, the percentage hospital admissions due to respiratory diseases predicted by influenza was 0.1%, 4.8% and 4.4%, respectively for the age groups 0-14 years, 50-64 years and 65 years and older (table4.2). The highest percentages were found in the seasons 2001/2002 and 2004/2005 (table A18). The percentage hospitalisations due to pneumonia and influenza predicted by influenza varied between 2.6 and 5.9% (table 4.2).

Spain
The number of hospitalisations due to pneumonia and influenza predicted by influenza activity varied between 8.4% and 12.3% (table 4.2). The highest percentage was found in the season 2004/2005 in the age group 50-64 years old (24.1%).

4.4 Summary of the main results

In summary, the percentages of deaths and hospitalizations in the five countries varied between the following values:

1. *All cause morality*
   The percentage of all cause mortality caused by influenza activity was highest in the age group 65 years and older (between 3.2 and 7.4%). The range of the percentages for the age groups 0-14 years and 50-64 years were 0.3-0.5% and 1.7-3.4%, respectively.
2. *Mortality due to respiratory diseases*
   The percentage of mortality due to respiratory disease caused by influenza activity was equal for the age groups 50-64 years and 65 years and older: 9.4-19.4% versus 9.4-19.3%.

3. *Mortality due to pneumonia and influenza*
   The percentage of mortality due to pneumonia and influenza caused by influenza activity was almost equal for the age groups 50-64 years and 65 years and older: 11.8-24.5% versus 12.1-25.1%.
4. *Hospitalizations due to respiratory diseases*
   The percentage of hospital admissions due to respiratory disease caused by influenza activity was highest in the age group 65 years and older (between 3.8 and 5.1%). The range of the percentages for the age groups 0-14 years and 50-64 years were 0.0-0.1% and 2.7-4.8%, respectively.
5. *Hospitalizations due to pneumonia and influenza*
   The percentage of hospital admissions due to pneumonia and influenza caused by influenza activity in the age groups 0-14 years, 50-64 years and 65 years and older were 0.9-8.4%, 3.3-12.3% and 4.3-10.9%, respectively.

5 General discussion

The objective of this study was to investigate the age-specific impact of seasonal influenza epidemics on hospital admissions and deaths in five European countries: the Netherlands, France, England, Portugal and Spain. For the age categories 0-14 years, 50-64 years and 65 years and older the percentage of deaths and hospitalizations caused by influenza activity was calculated for all countries in influenza seasons between 1996 and 2006.

For this study a new statistical model was used to calculate the influence of influenza activity on hospital admissions and mortality. Unlike previously used methods, such as the Serfling method [18], a Poisson model with Fourier series was used with the number of ILI contacts in general practices as the independent variable. This makes a comparison with previous studies difficult.

Comparison with other studies (rates per 100,000 population)
We compared our findings with other published national estimates (Australia [10], England and Wales [2], Hong Kong [19], Italy [3], Singapore [20], Spain [21], the US [9, 11, 12] and found that, on average, we had conservative estimates of excess hospitalisations and mortality (see Annex 2, table 24). The analysis in Spain [21] uses the same data but a different model (a Generalised Linear Model) and found quite similar levels of excess mortality for the age group 65+.

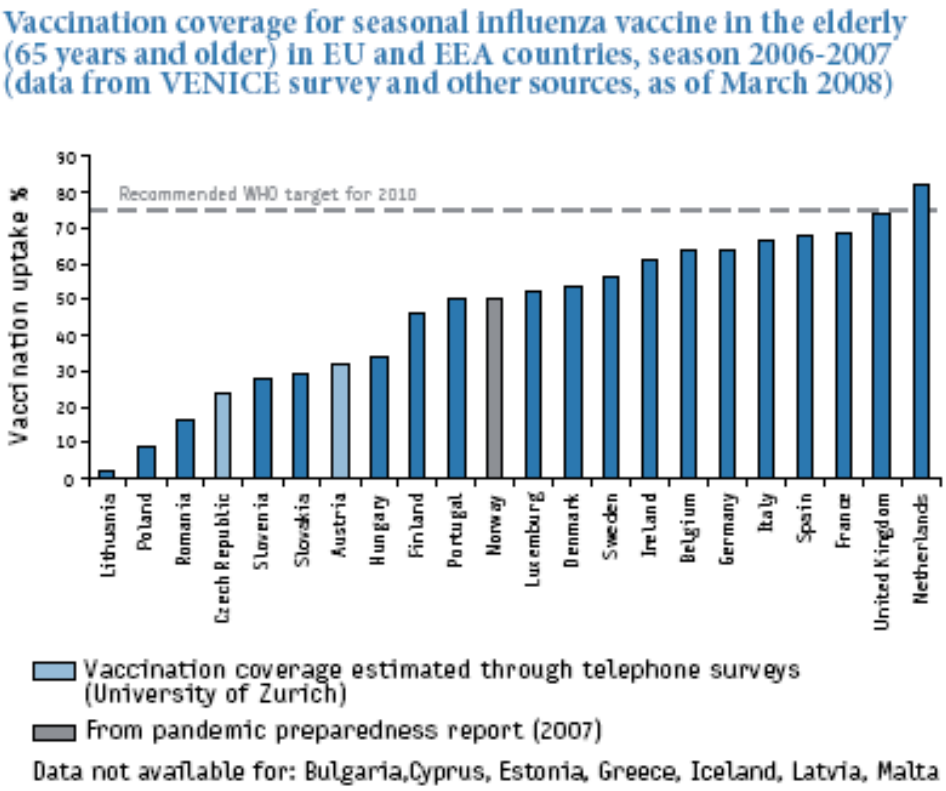
Comparison with other studies (% of total hospitalisations/deaths)
We found three studies (Czech Republic [22], England and Wales [2] and the US [11]) that calculated national estimates for the percentage of influenza-attributable to mortality and no studies for hospitalisations (see Annex 2, table 22). It is difficult to compare these studies to our findings as they present data for all ages and we had estimates for three different age groups, but they appear to be reasonably similar for all cause mortality (<5%).

Besides the model used, there are other reasons that make inter-country comparisons difficult: 1) variations in the years studied, 2) inclusion of more independent variables, 3) the quality of the data, 4) the definitions used for influenza activity and the diagnoses which resulted in death or hospital admission, and 5) access to hospitalised care.

Influenza activity was the only independent variable in our statistical model and it is likely that the results from the present study overestimate the influence of influenza on mortality and hospital admissions. In the future, the model should be optimized by correcting for potential confounders, such as, the degree of vaccination in specific age groups, RSV activity, the influence of the weather (especially the temperature and absolute humidity) and the frequency of cardiovascular diseases.

Vaccination

Influenza vaccination has an impact on the burden of disease, especially among persons aged 65 and older (65+) [24], which is a high risk group vaccinated in all five countries. Of the five countries included in our study, vaccination levels are very similar for the Netherlands, United Kingdom, France and Spain (roughly 70-80%) but much lower for Portugal (roughly 50%) (see Figure below) [6] and this may affect the burden of disease estimates for Portugal (increasing the estimates compared to the other four countries). Although from this analysis there is no difference between the percentage of deaths and hospitalizations predicted by influenza in the +65 age group in comparison with other countries with much higher vaccine coverage rate.



The targeted vaccination of one age group (65+) also affects our age group comparisons (0-9, 50-64 versus 65+). The targeted vaccination results in an underestimation of the results in the 65+ age group and makes a direct comparison with the two other age groups difficult.

Role of other respiratory viruses such as RSV

Our study was not able to correct for RSV activity during the winter. In seasons when RSV and influenza circulated in the same period (there was an 'overlap'), a part of the deaths and hospital admissions due to influenza could be caused by RSV instead, especially in very young children and those aged 65+ [25].

Role of weather (temperature)and cardiovascular diseases
Compared with the course of mortality, cardiovascular diseases and the temperature [26, 27] show similar curves over time, which makes it likely that these variables confound the relation between influenza and mortality.

In conclusion, besides the above mentioned limitations of this study and fluctuations per country and influenza seasons, we found that only a small part of the hospital admissions and death in the influenza periods of the five participating countries are caused by influenza. For a better estimate of the impact of influenza on mortality and hospital admissions confounding factors, such as RSV activity, temperature and the degree of vaccination, should be added to the statistical model.

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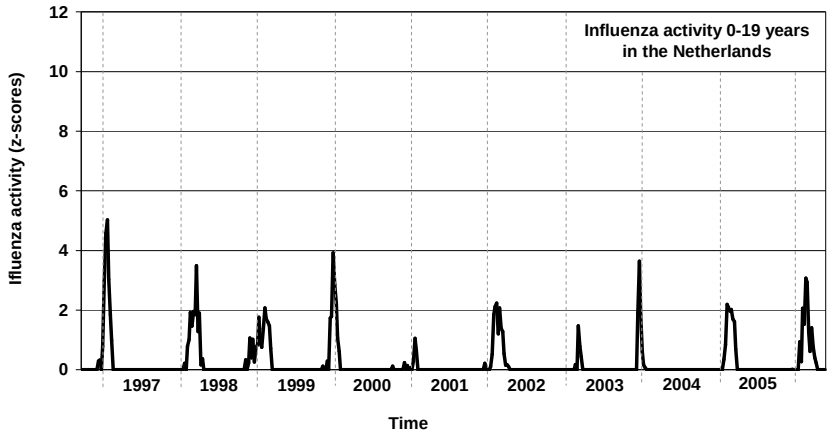
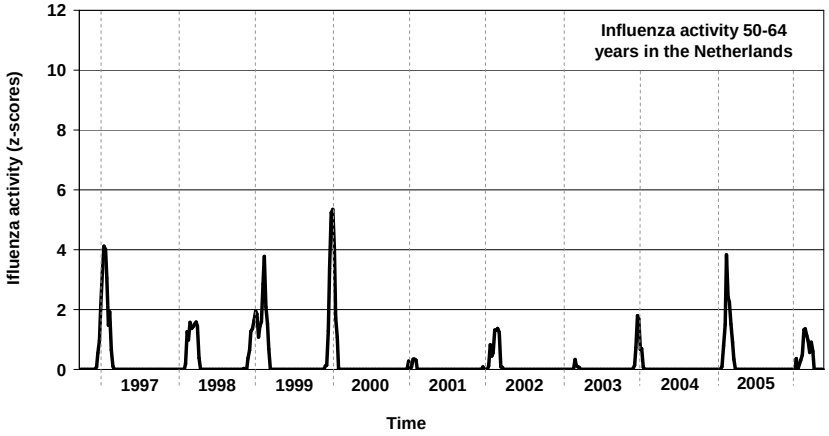
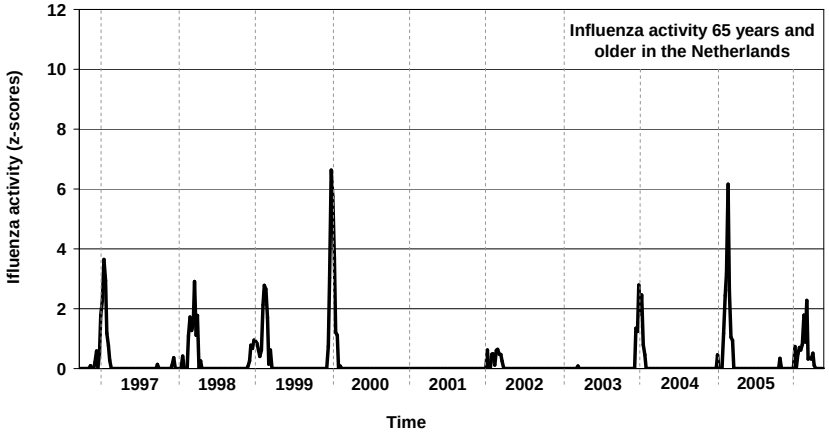
Annex 1: Graphs

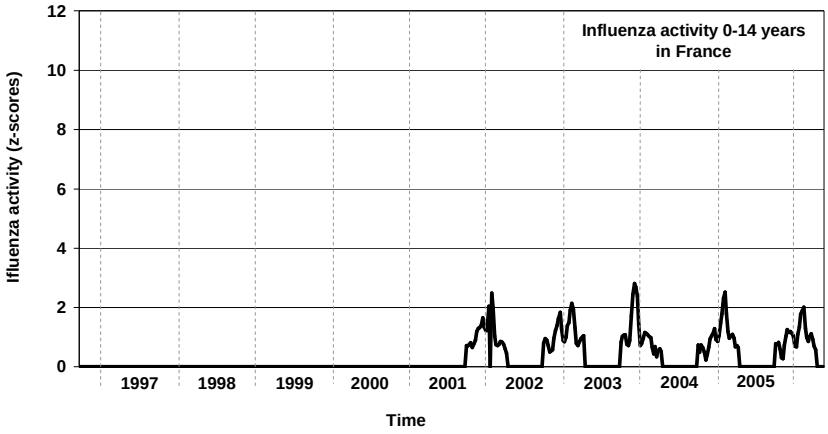
Graph A1A: Influenza activity in the Netherlands for the age categories 0-19 years, 50-64 years and 65 years and older

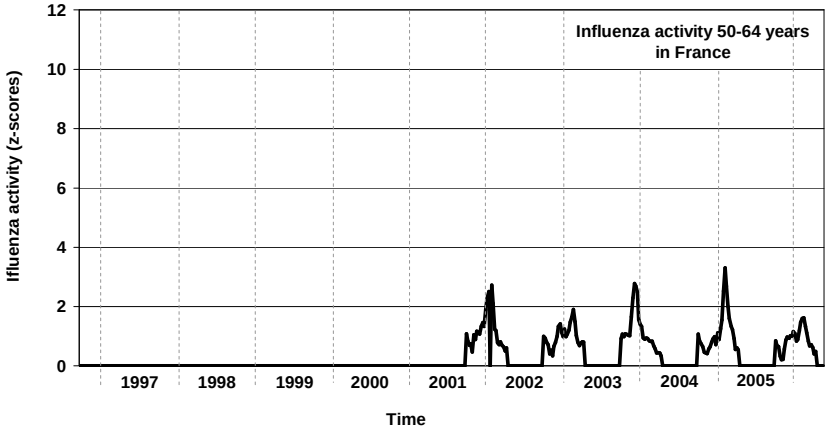


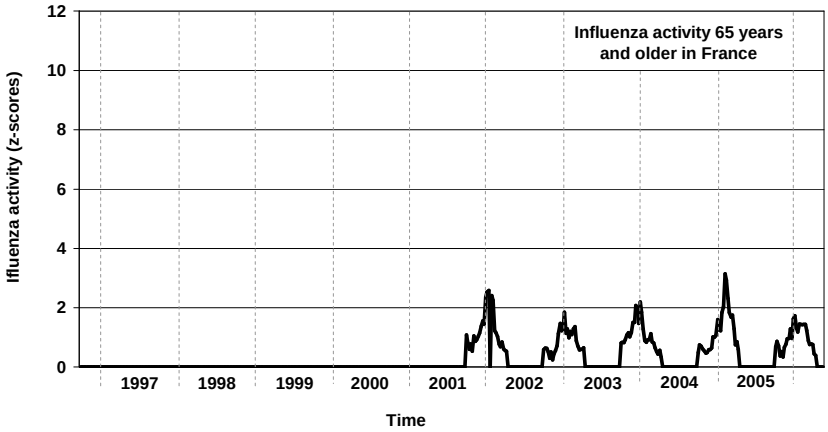




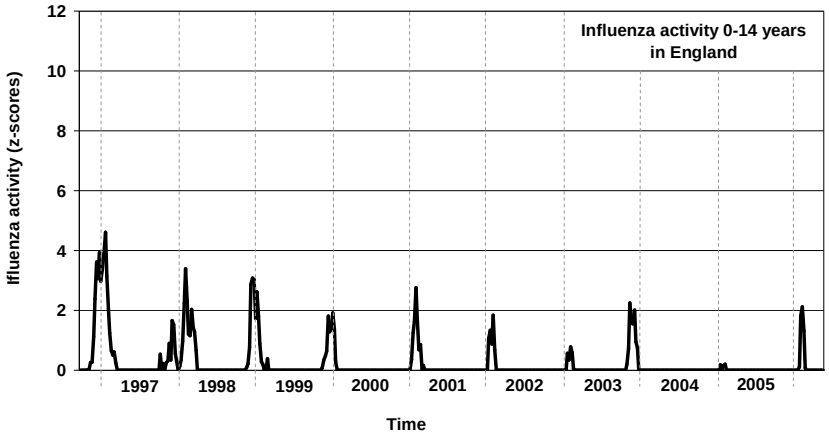
Graph A1B: Influenza activity in France for the age categories 0-14 years, 50-64 years and 65 years and older

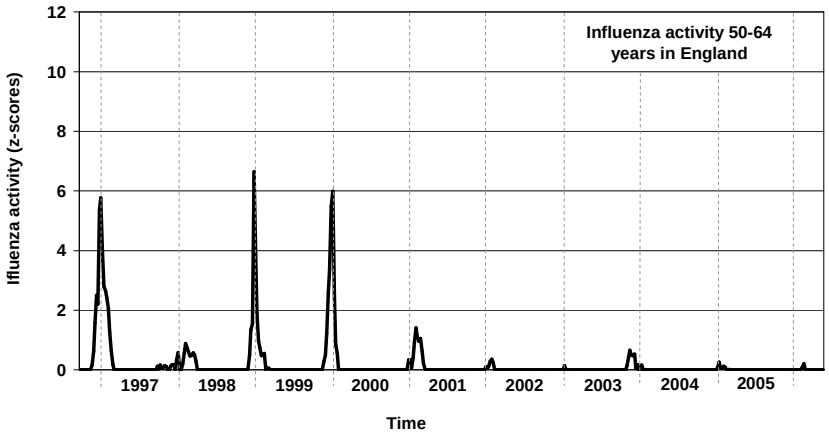


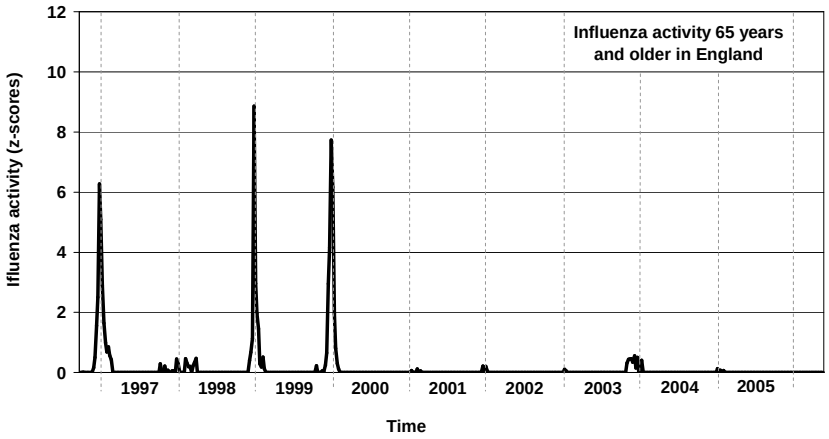




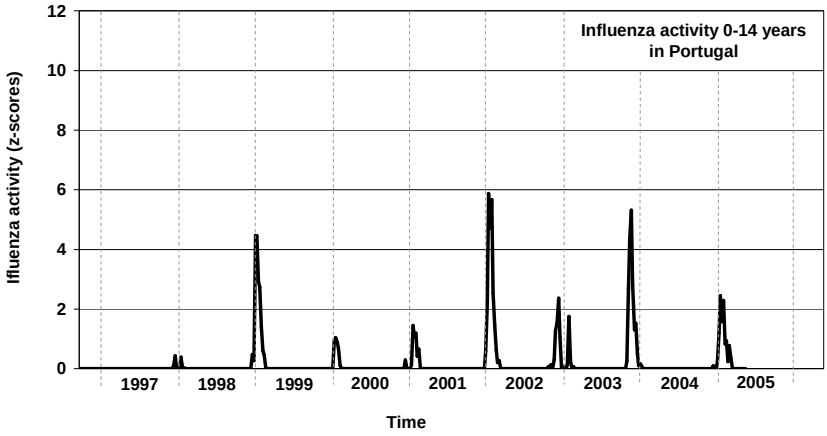
Graph A1C: Influenza activity in England for the age categories 0-14 years, 50-64 years and 65 years and older

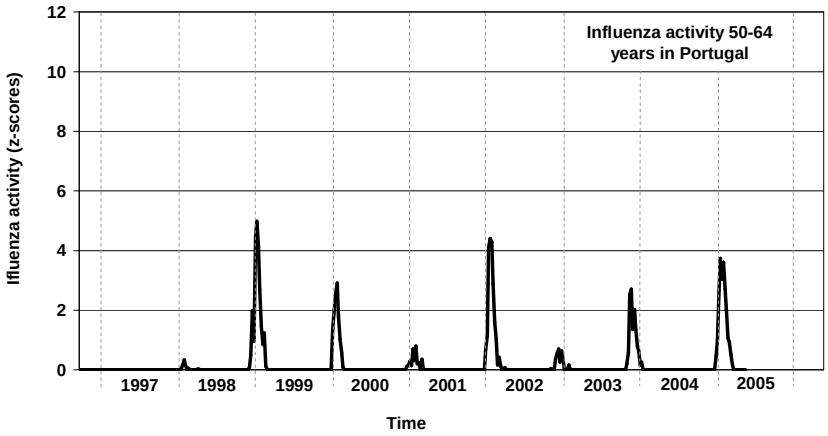


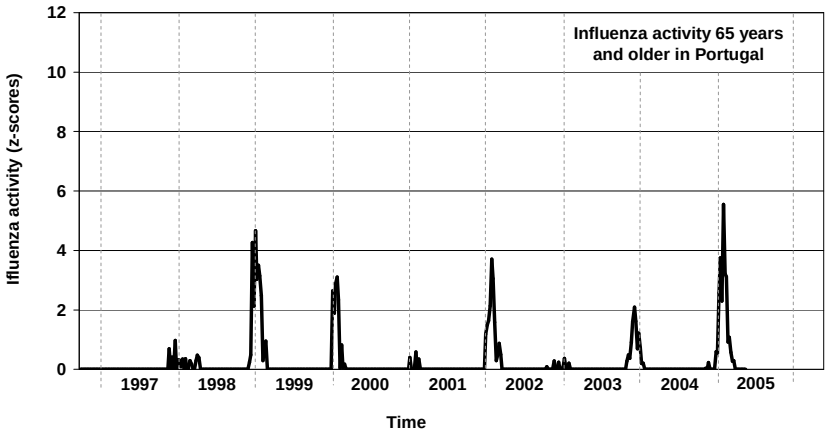




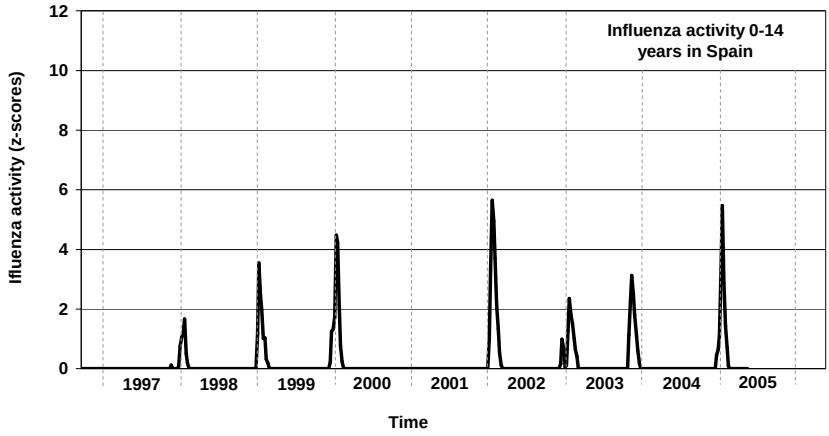
Graph A1D: Influenza activity in Portugal for the age categories 0-14 years, 50-64 years and 65 years and older

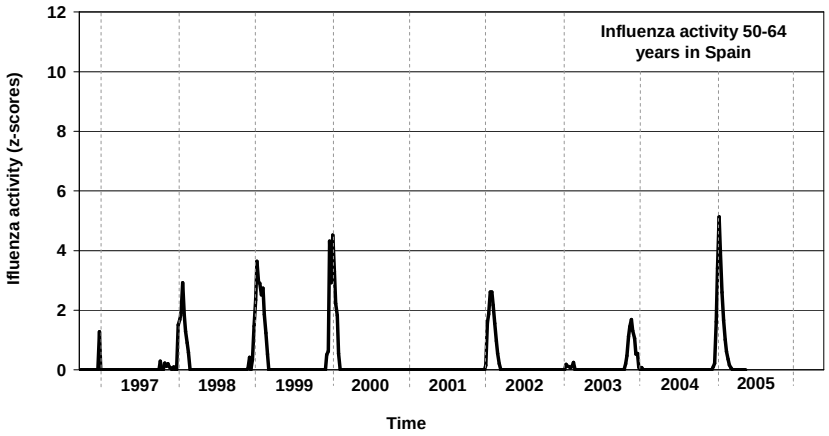


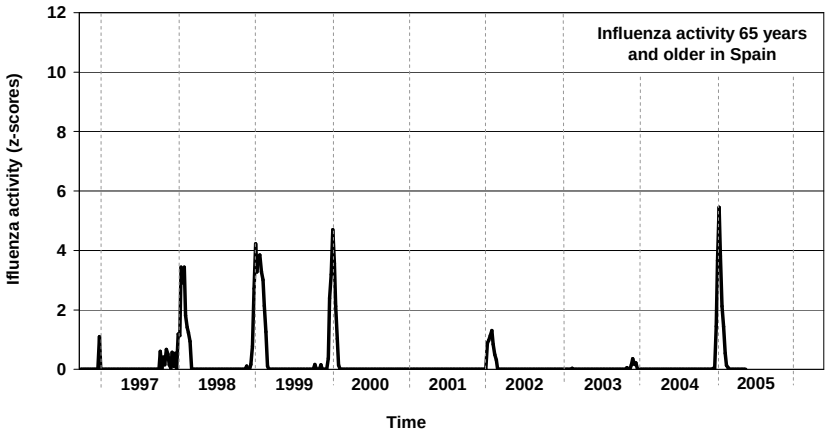




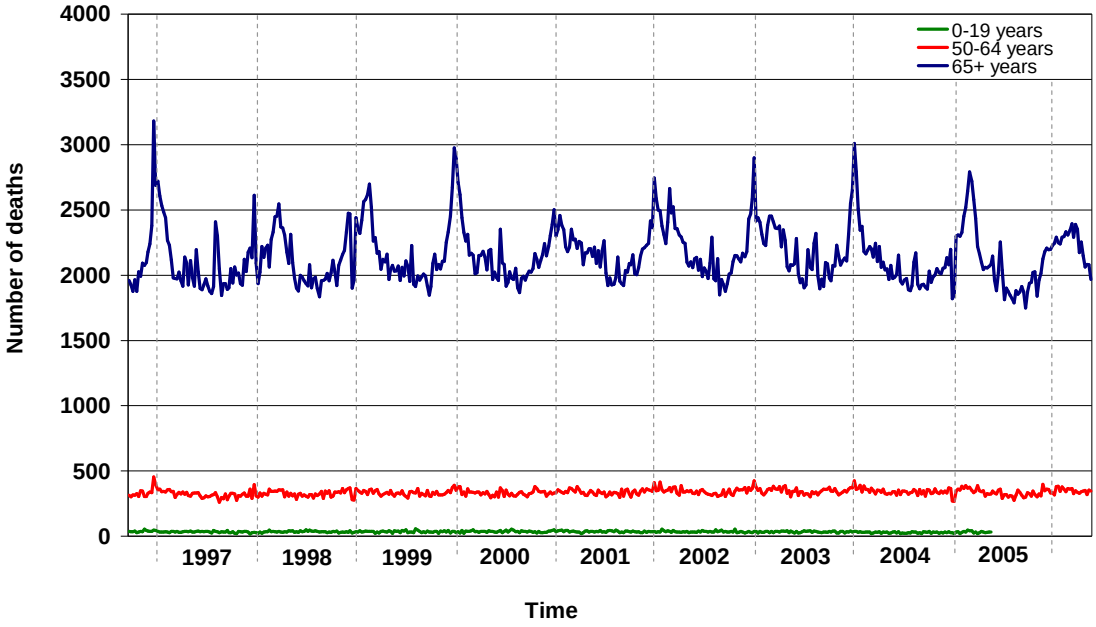
Graph A1E: Influenza activity in Spain for the age categories 0-14 years, 50-64 years and 65 years and older



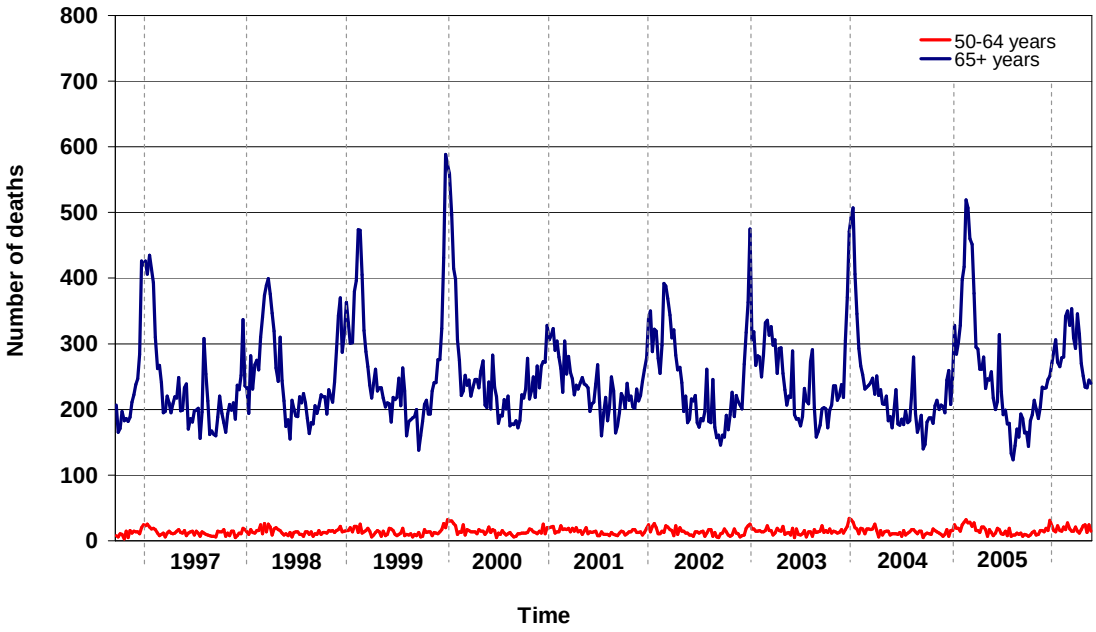




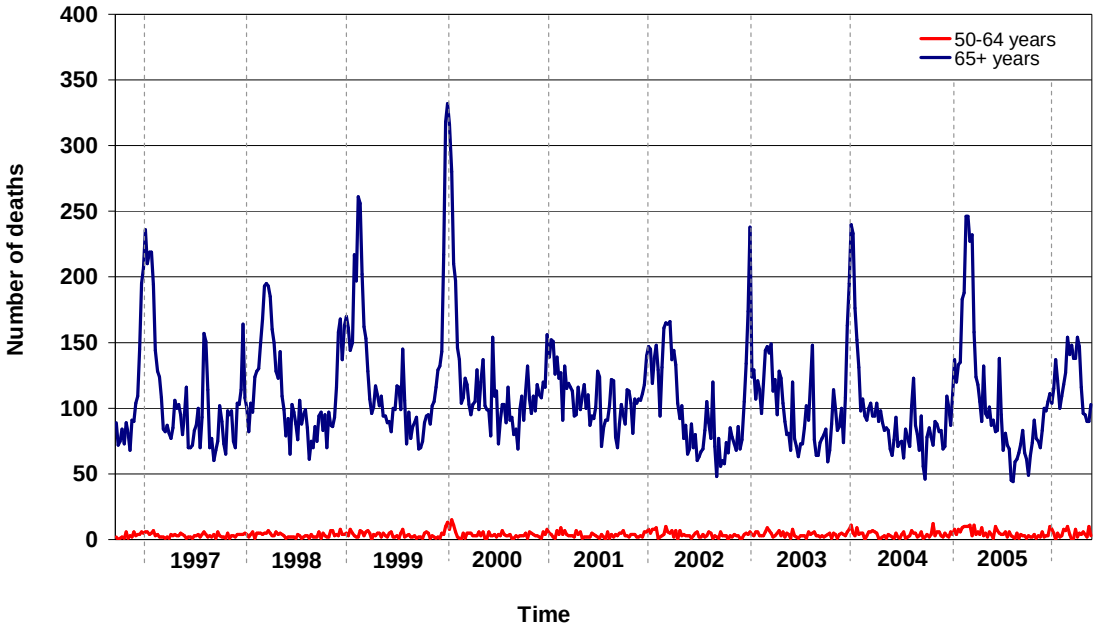
Graph A2: All cause mortality in the Netherlands by age category



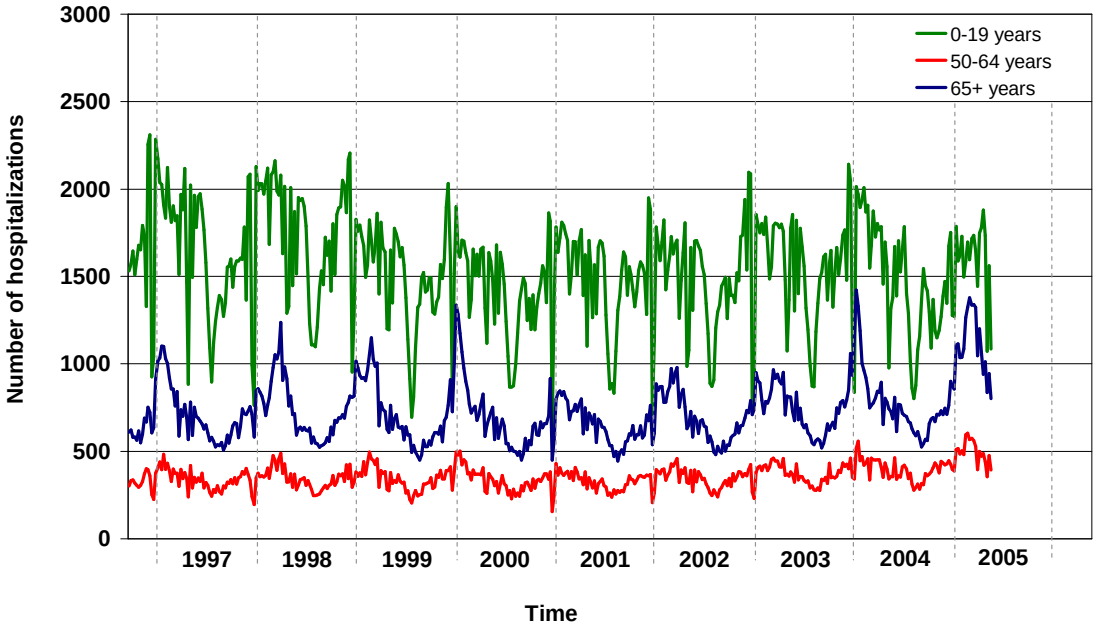
Graph A3: Mortality caused by respiratory diseases in the Netherlands by age category



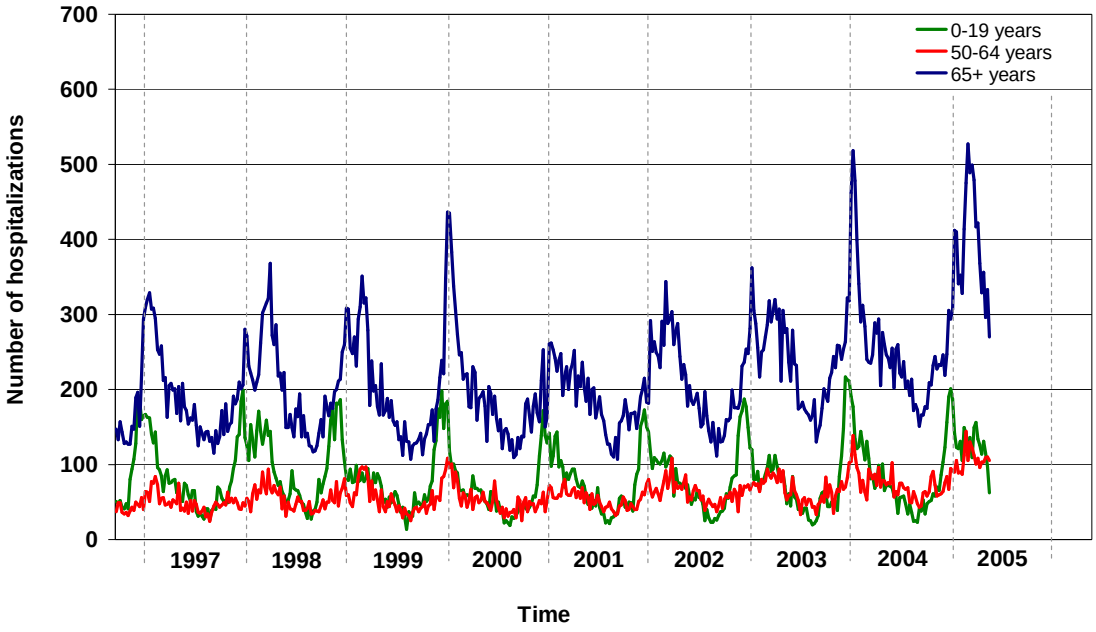
Graph A4: Mortality caused by pneumonia and influenza in the Netherlands by age category



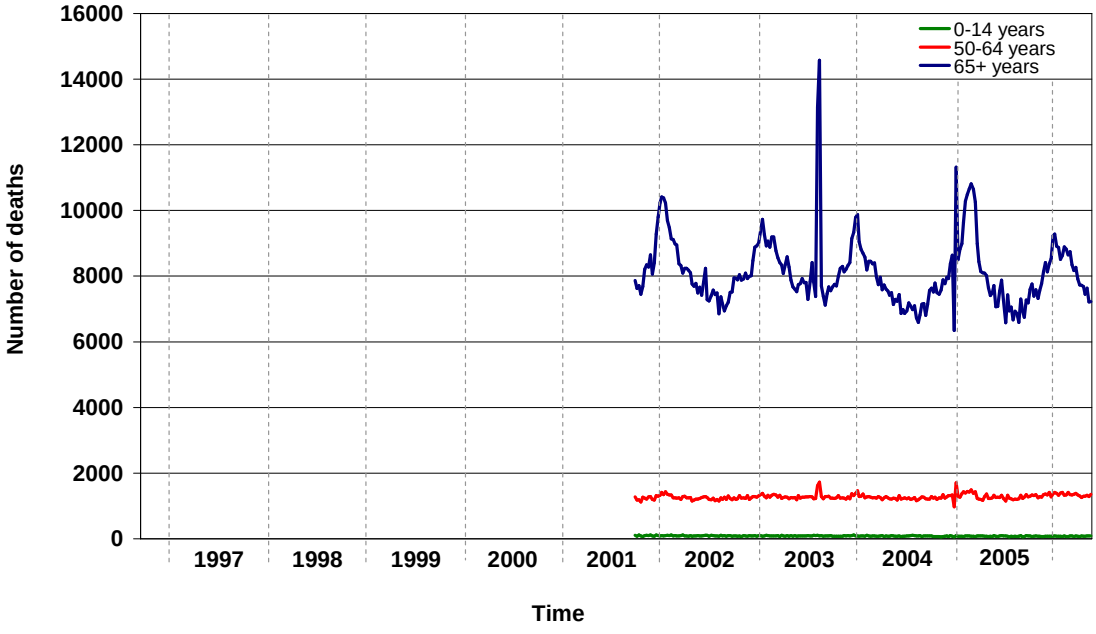
Graph A5: Hospitalizations caused by respiratory diseases in the Netherlands by age category



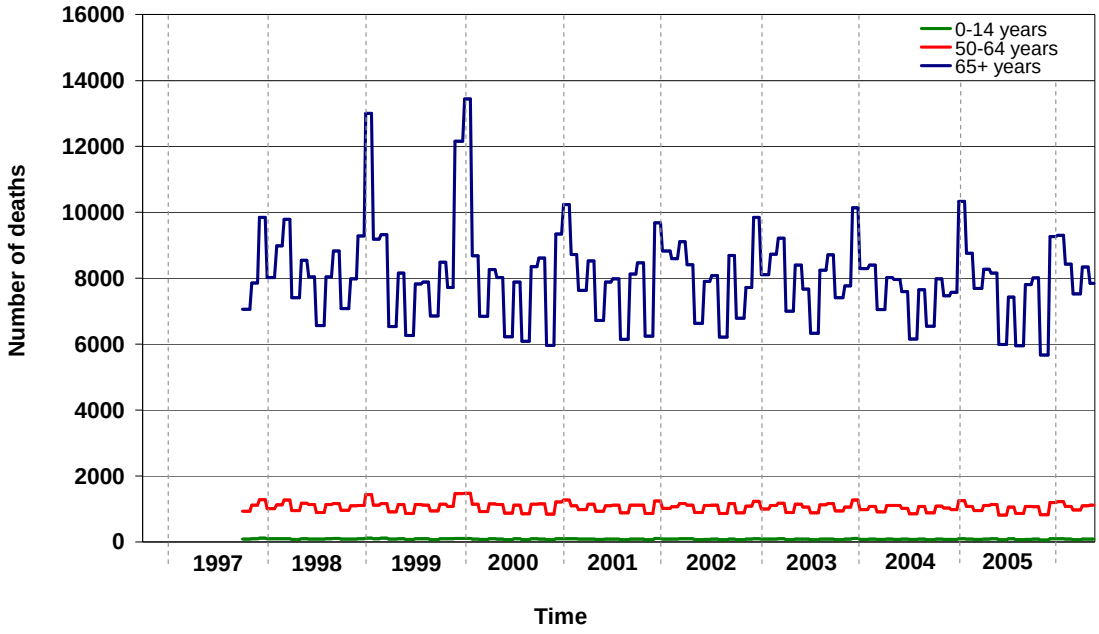
Graph A6: Hospitalizations caused by pneumonia and influenza in the Netherlands by age category



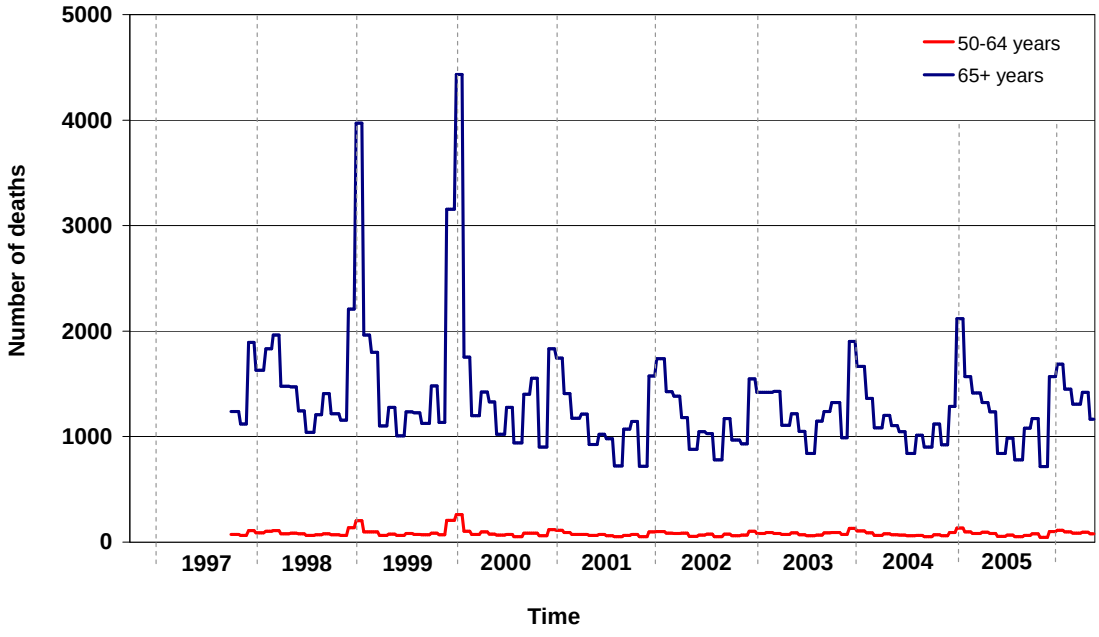
Graph A7: All cause mortality in France by age category



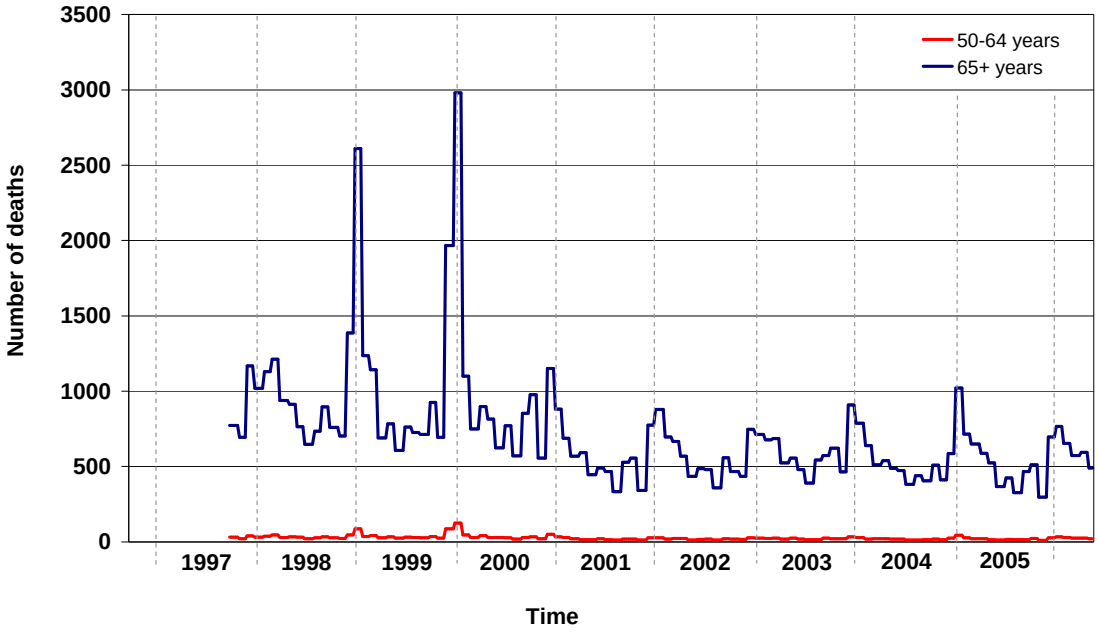
Graph A8: All cause mortality in England by age category



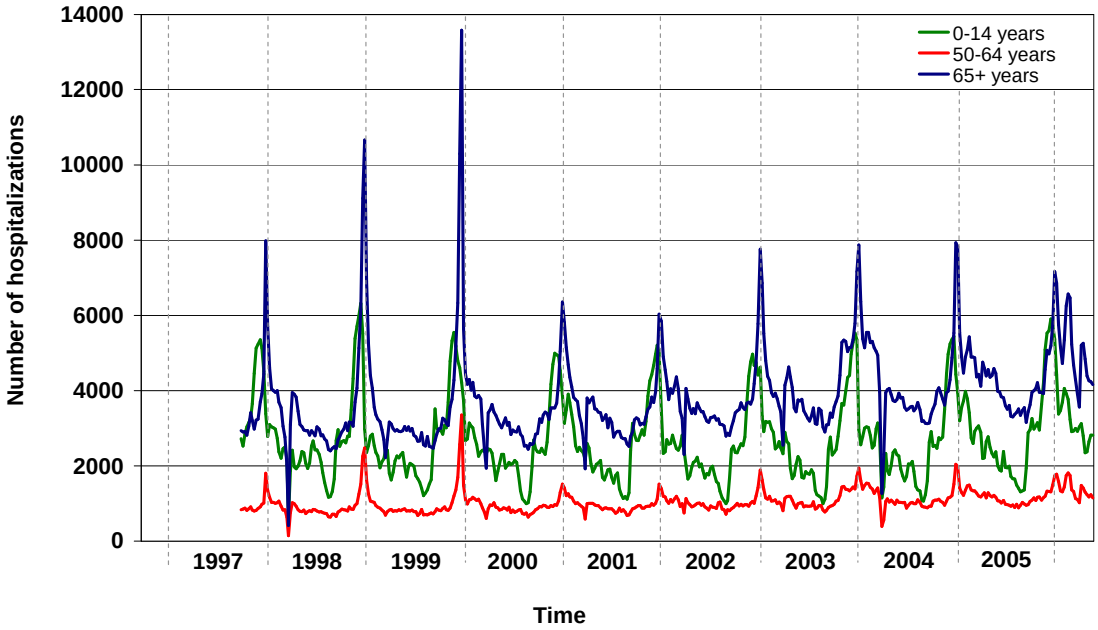
Graph A9: Mortality caused by respiratory diseases in England by age category



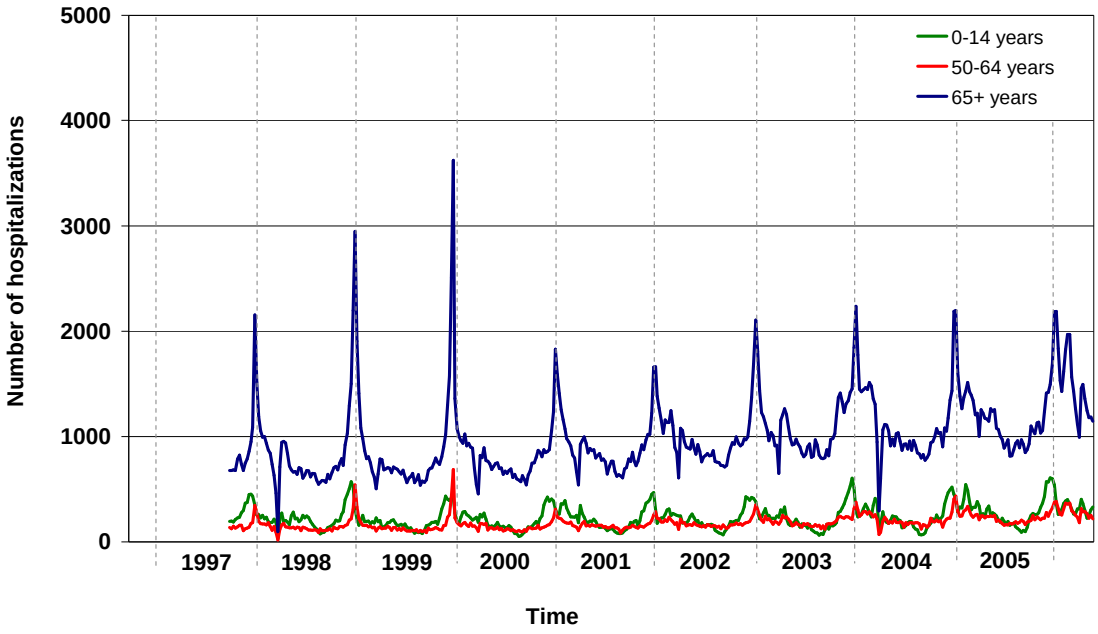
Graph A10: Mortality caused by pneumonia and influenza in England by age category



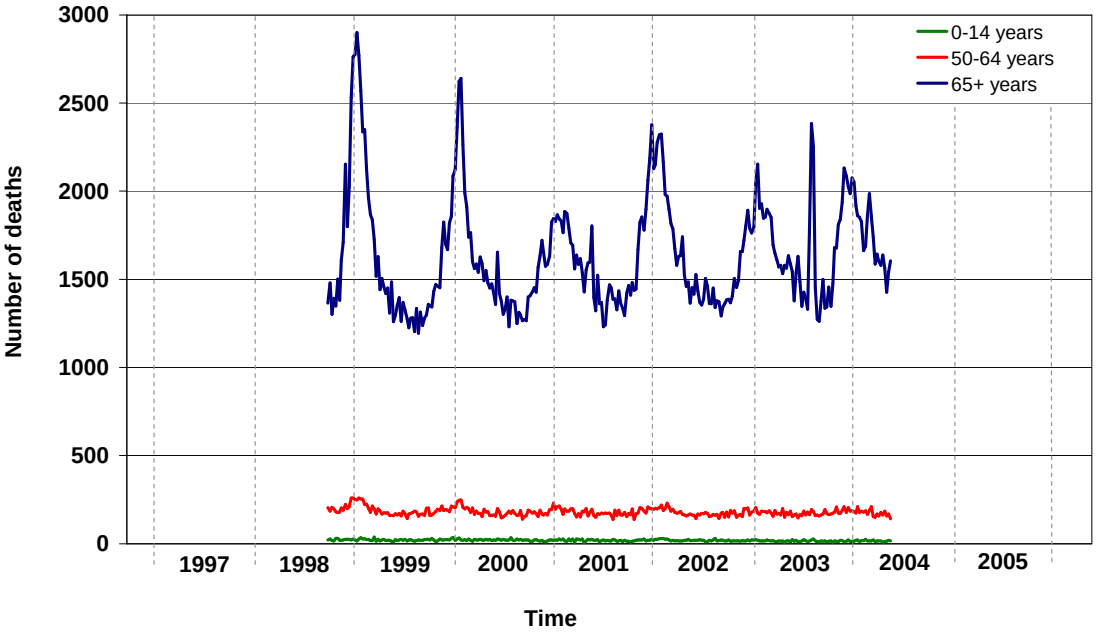
Graph A11: Hospitalizations caused by respiratory diseases in England by age category



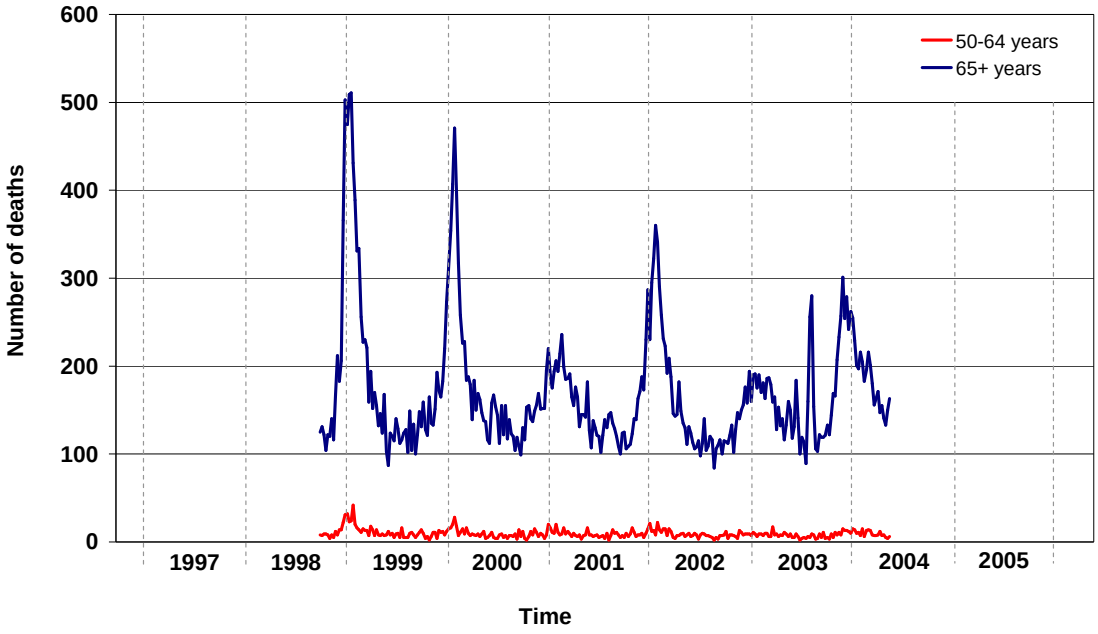
Graph A12: Hospitalizations caused by pneumonia and influenza in England by age category



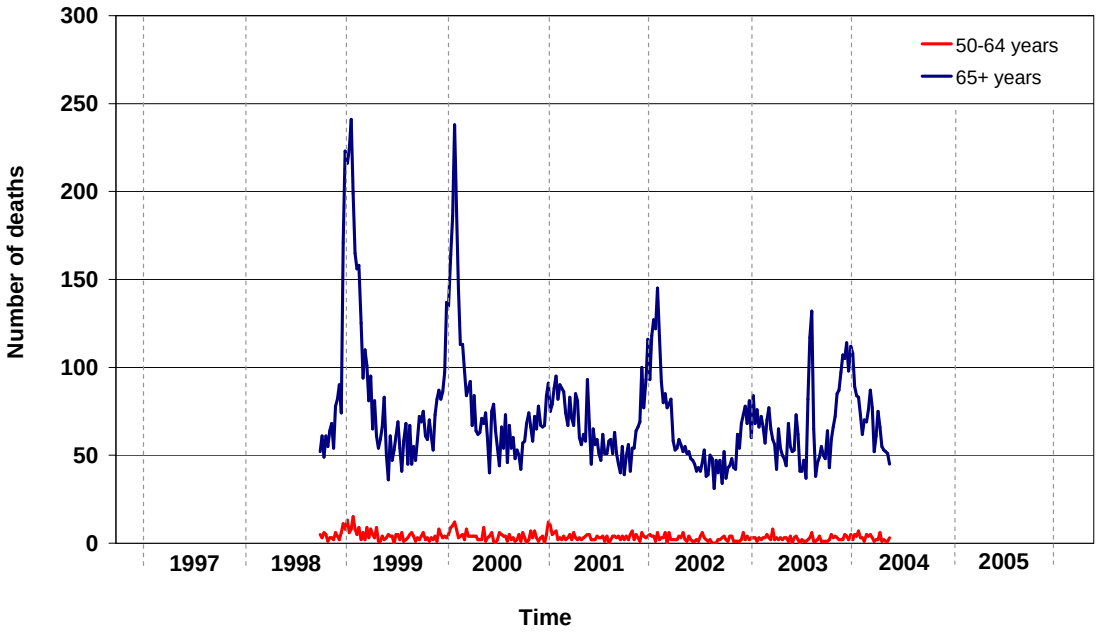
Graph A13: All cause mortality in Portugal by age category



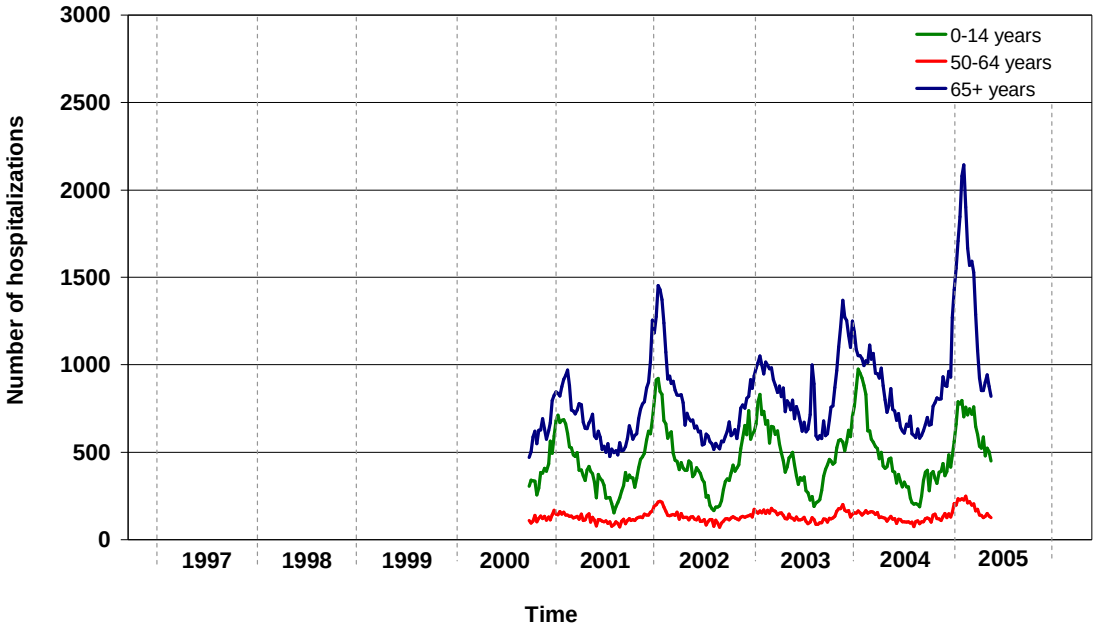
Graph A14: Mortality caused by respiratory diseases in Portugal by age category



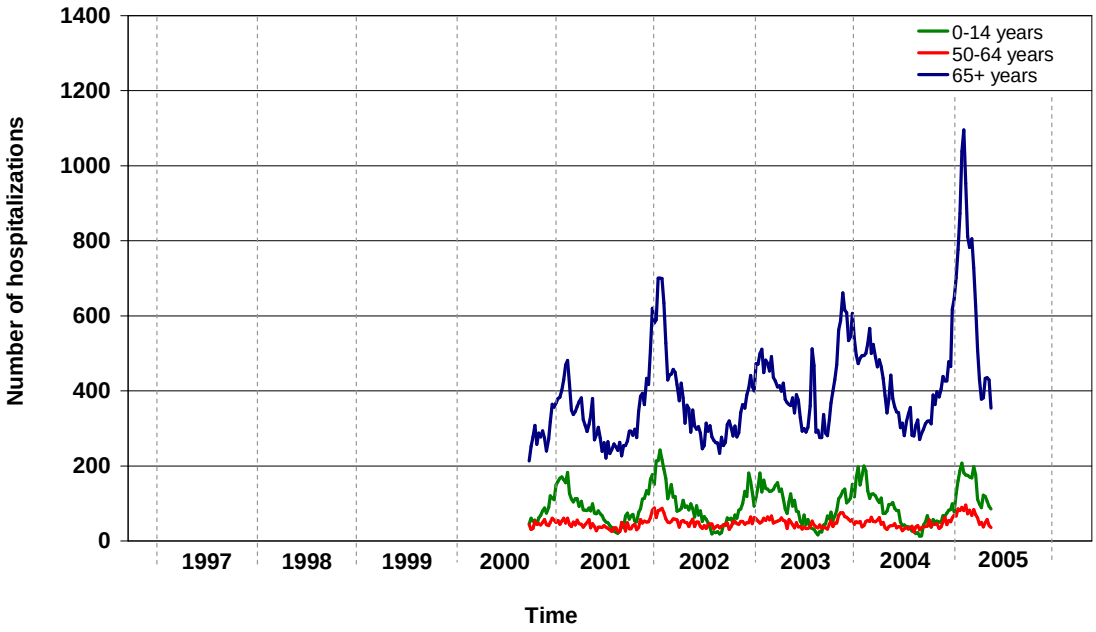
Graph A15: Mortality caused by pneumonia and influenza in Portugal by age category



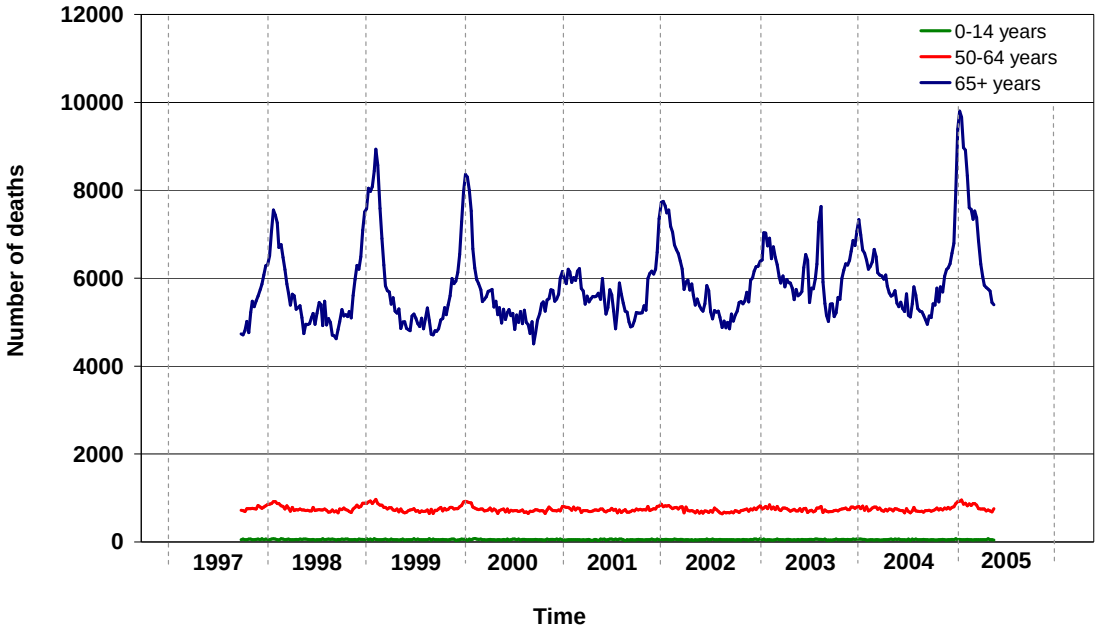
Graph A16: Hospitalizations caused by respiratory diseases in Portugal by age category



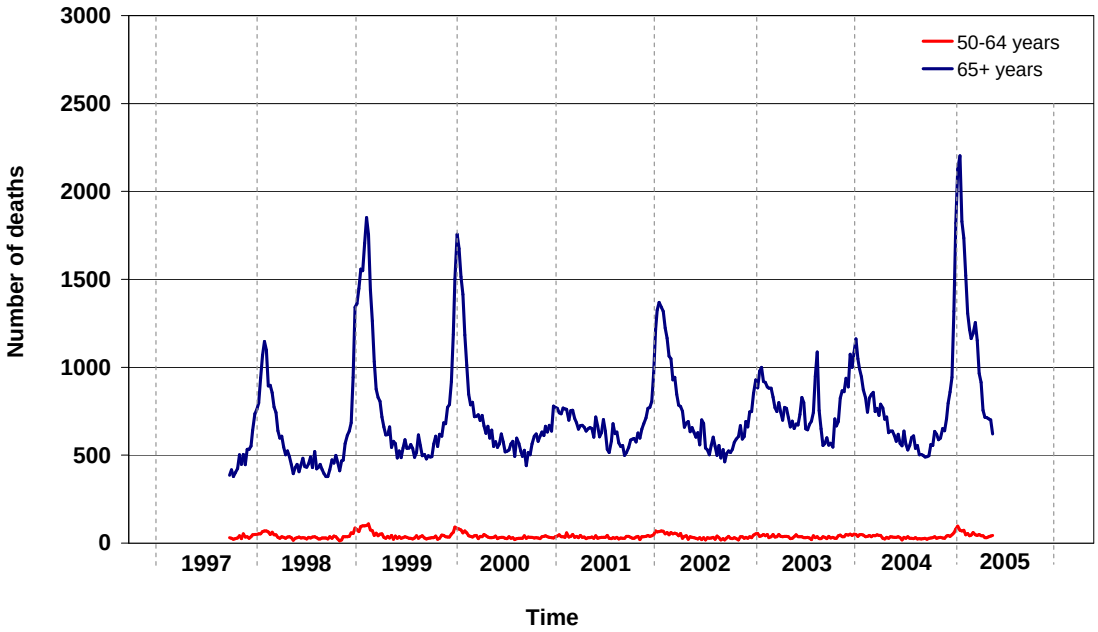
Graph A17: Hospitalizations caused by pneumonia and influenza in Portugal by age category



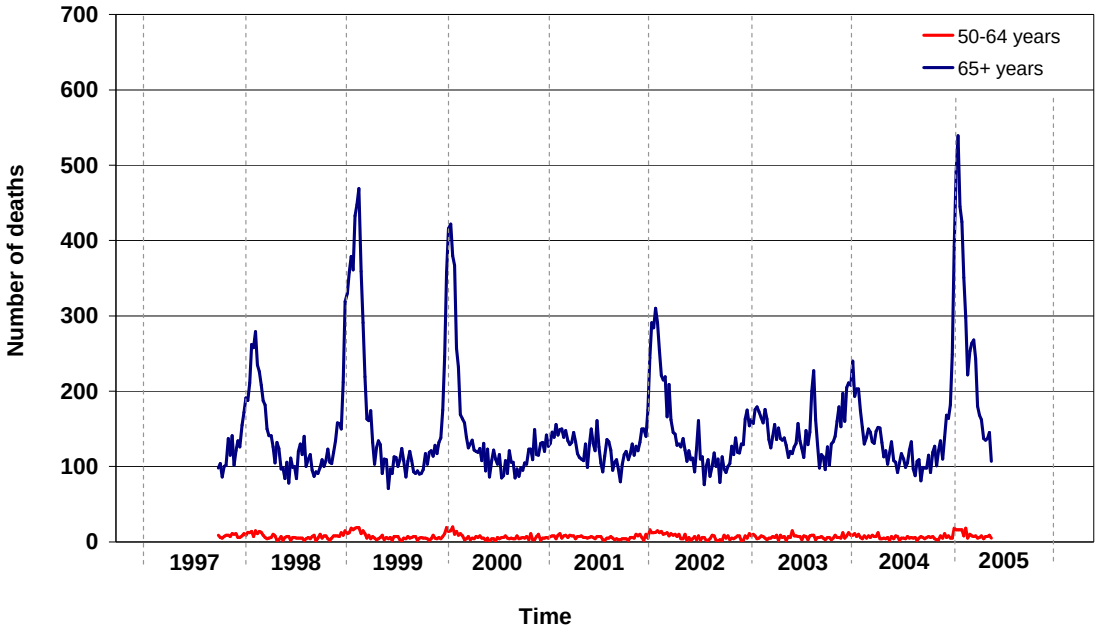
Graph A18: All cause mortality in Spain by age category



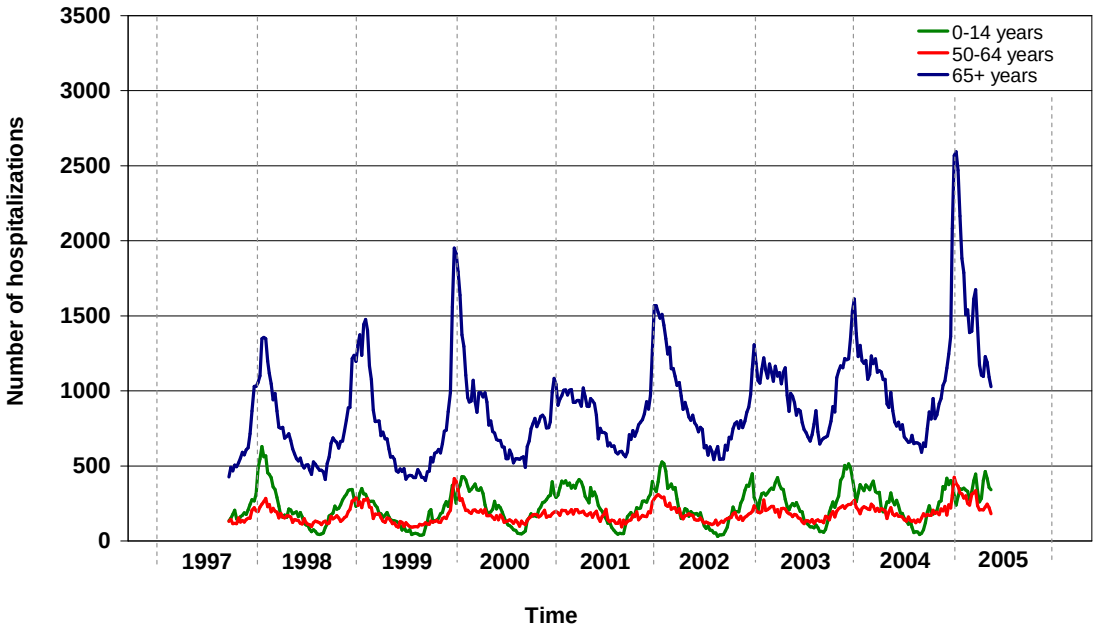
Graph A19: Mortality caused by respiratory diseases in Spain by age category



Graph A20: Mortality caused by pneumonia and influenza in Spain by age category



Graph A21: Hospitalizations caused by pneumonia and influenza in Spain by age category



Annex 2: Tables

Table A1: Number of total deaths predicted by influenza activity in the Netherlands per influenza-season

Year (influenza period)	0-19 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
1996/1997 (week 1–7)	256	1.7 (0.7%)	2,597	124.4 (4.8%)	18,648	1481.5 (7.9%)
1997/1998 (week 4–14)	377	1.3 (0.4%)	3,713	64.6 (1.7%)	24,919	1107.4 (4.4%)
1998/1999 (week 52–9)	344	1.2 (0.3%)	3,324	131.3 (4.0%)	23,857	1431.0 (6.0%)
1999/2000 (week 50–4)	232	1.3 (0.6%)	2,568	147.1 (5.7%)	18,648	2662.7 (14.3%)
2000/2001 (week 52–8)	384	0.2 (0.0%)	3,042	8.9 (0.3%)	21,130	0.0 (0.0%)
2001/2002 (week 5–13)	344	1.3 (0.4%)	3,202	43.0 (1.3%)	21,710	359.4 (1.7%)
2002/2003 (week 9–15)	237	0.2 (0.1%)	2,547	3.8 (0.2%)	16,627	8.9 (0.1%)
2003/2004 (week 49–1)	173	0.7 (0.4%)	1,874	34.4 (1.8%)	12,636	853.9 (6.8%)
2004/2005 (week 4–10)	249	0.8 (0.3%)	2,594	84.2 (3.2%)	17,748	1935.3 (10.9%)
2005/2006 (week 6–12)	---	---	2,477	44.8 (1.8%)	16,352	719.5 (4.4%)
Total	2,596	9 (0.3%)	27,938	687 (2.5%)	192,275	10,560 (5.5%)

Table A2: Number of deaths to respiratory diseases predicted by influenza activity in the Netherlands per influenza-season

Year (influenza period)	50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)
1996/1997 (week 1–7)	150	37.3 (24.9%)	2,920	521.9 (17.9%)
1997/1998 (week 4–14)	184	17.0 (9.2%)	3,323	362.0 (10.9%)
1998/1999 (week 52–9)	177	40.2 (22.7%)	3,625	530.6 (14.6%)
1999/2000 (week 50–4)	169	53.1 (31.4%)	3,246	1127.9 (34.7%)
2000/2001 (week 52–8)	157	2.5 (1.6%)	2,678	0.0 (0.0%)
2001/2002 (week 5–13)	147	11.9 (8.1%)	2,952	119.3 (4.0%)
2002/2003 (week 9–15)	111	1.1 (1.0%)	2,166	3.0 (0.1%)
2003/2004 (week 49–1)	117	10.9 (9.3%)	1,857	295.3 (15.9%)
2004/2005 (week 4–10)	173	27.1 (15.7%)	2,930	746.3 (25.5%)
2005/2006 (week 6–12)	134	13.9 (10.4%)	2,255	253.4 (11.2%)
Total	1,519	215 (14.2%)	27,952	3,960 (14.2%)

Table A3: Number of deaths to pneumonia and influenza predicted by influenza activity in the Netherlands per influenza-season

Year (influenza period)	50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)
1996/1997 (week 1–7)	39	12.9 (33.1%)	1,480	319.3 (21.6%)
1997/1998 (week 4–14)	49	5.8 (11.8%)	1,564	225.5 (14.4%)
1998/1999 (week 52–9)	43	12.7 (29.5%)	1,856	314.3 (16.9%)
1999/2000 (week 50–4)	56	18.6 (33.2%)	1,738	727.8 (41.9%)
2000/2001 (week 52–8)	44	0.9 (2.1%)	1,229	0.0 (0.0%)
2001/2002 (week 5–13)	47	4.3 (9.1%)	1,295	66.1 (5.1%)
2002/2003 (week 9–15)	37	0.4 (1.0%)	912	1.7 (0.2%)
2003/2004 (week 49–1)	32	4.0 (12.4%)	780	161.7 (20.7%)
2004/2005 (week 4–10)	64	9.3 (14.5%)	1,358	440.0 (32.4%)
2005/2006 (week 6–12)	38	4.9 (12.8%)	964	133.7 (13.9%)
Total	449	74 (16.5%)	13,176	2,390 (18.1%)

Table A4: Number of total deaths predicted by influenza activity in France per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
2001/2002 (week 52–6)	690	1.8 (0.3%)	9,509	250.7 (2.6%)	70,232	4857.5 (6.9%)
2002/2003 (week 4–10)	636	1.7 (0.3%)	9,193	142.5 (1.6%)	63,282	1617.2 (2.6%)
2003/2004 (week 46–50)	479	1.9 (0.4%)	6,337	199.2 (3.1%)	42,216	1746.5 (4.1%)
2004/2005 (week 1–9)	746	2.1 (0.3%)	12,820	319.8 (2.5%)	89,511	5931.2 (6.6%)
2005/2006 (week 1–9)	705	1.4 (0.2%)	12,365	146.6 (1.2%)	79,310	3056.3 (3.9%)
Total	3,256	9 (0.3%)	50,224	1059 (2.1%)	344,551	17,209 (5.0%)

Table A5: Number of total deaths predicted by influenza activity in England per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
1997/1998 (week 3–13)	1,107	4.9 (0.4%)	12,612	133.7 (1.1%)	99,160	736.7 (0.7%)
1998/1999 (week 52–8)	939	4.1 (0.4%)	11,275	518.4 (4.6%)	98,027	9488.3 (9.7%)
1999/2000 (week 48–2)	756	2.4 (0.3%)	10,253	593.1 (5.8%)	87,647	11801.5 (13.5%)
2000/2001 (week 3–9)	640	2.5 (0.4%)	7,896	159.4 (2.0%)	62,981	98.2 (0.2%)
2001/2002 (week 51–3)	462	0.3 (0.1%)	5,525	6.9 (0.1%)	45,835	203.0 (0.4%)
2002/2003 (week 2–12)	976	0.6 (0.1%)	11,934	3.8 (0.0%)	94,962	66.6 (0.1%)
2003/2004 (week 43–49)	615	2.2 (0.4%)	7,395	68.3 (0.9%)	56,015	1005.9 (1.8%)
2004/2005 (week 52–11)	1,046	0.1 (0.0%)	13,131	16.5 (0.1%)	106,990	111.0 (0.1%)
2005/2006 (week 1–9)	812	1.4 (0.2%)	10,136	7.3 (0.1%)	78,420	0.0 (0.0%)
Total	7,353	19 (0.3%)	90,157	1,507 (1.7%)	730,037	23,511 (3.2%)

Table A6: Number of deaths to respiratory diseases predicted by influenza activity in England per influenza-season

Year (influenza period)	50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%
1997/1998 (week 3–13)	1,103	54.4 (4.9%)	20,071	330.0 (1.6%
1998/1999 (week 52–8)	1,333	311.7 (23.4%)	25,958	5947.3 (22.9%
1999/2000 (week 48–2)	1,555	359.2 (23.1%)	24,641	7043.3 (28.6%
2000/2001 (week 3–9)	661	67.4 (10.2%)	10,293	41.1 (0.4%
2001/2002 (week 51–3)	493	3.2 (0.6%)	8,368	81.5 (1.0%
2002/2003 (week 2–12)	941	1.8 (0.2%)	15,648	31.3 (0.2%
2003/2004 (week 43–49)	606	25.1 (4.1%)	8,505	353.2 (4.2%
2004/2005 (week 52–11)	1,256	7.7 (0.6%)	20,268	49.4 (0.2%
2005/2006 (week 1–9)	916	3.0 (0.3%)	13,855	0.0 (0.0%
Total	8,864	833 (9.4%)	147,607	13,877 (9.4%

Table A7: Number of deaths to pneumonia and influenza predicted by influenza activity in England per influenza-season

Year (influenza period)	50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)
1997/1998 (week 3–13)	432	23.3 (5.4%)	12,421	235.5 (1.9%)
1998/1999 (week 52–8)	543	143.5 (26.4%)	16,776	4296.1 (25.6%)
1999/2000 (week 48–2)	685	164.1 (24.0%)	15,793	5061.2 (32.0%)
2000/2001 (week 3–9)	204	21.2 (10.4%)	5,084	23.6 (0.5%)
2001/2002 (week 51–3)	138	1.0 (0.8%)	4,189	44.5 (1.1%)
2002/2003 (week 2–12)	270	0.6 (0.2%)	7,614	17.2 (0.2%)
2003/2004 (week 43–49)	158	7.3 (4.6%)	4,016	189.2 (4.7%)
2004/2005 (week 52–11)	379	2.4 (0.6%)	9,482	25.8 (0.3%)
2005/2006 (week 1–9)	277	0.8 (0.3%)	6,258	0.0 (0.0%)
Total	3,086	364 (11.8%)	81,633	9,893 (12.1%)

Table A8: Number of total deaths predicted by influenza activity in Portugal per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
1998/1999 (week 51–5)	172	0.8 (0.5%)	1,745	75.4 (4.3%)	18,339	2125.8 (11.6%)
1999/2000 (week 1–7)	179	0.1 (0.0%)	1,549	21.0 (1.4%)	16,092	715.2 (4.4%)
2000/2001 (week 50–9)	249	0.2 (0.1%)	2,329	5.7 (0.2%)	21,573	97.7 (0.5%)
2001/2002 (week 2–6)	139	1.0 (0.7%)	1,011	60.3 (6.0%)	11,238	1166.9 (10.4%)
2002/2003 (week 46–4)	201	0.2 (0.1%)	1,994	6.4 (0.3%)	20,190	55.1 (0.3%)
2003/2004 (week 45–49)	74	0.5 (0.7%)	920	27.9 (3.0%)	9,804	450.7 (4.6%)
Total	1,014	3 (0.3%)	9,548	197 (2.1%)	97,236	4,611 (4.7%)

Table A9: Number of deaths to respiratory diseases predicted by influenza activity in Portugal per influenza-season

Year (influenza period)	50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)
1998/1999 (week 51–5)	188	34.6 (18.4%)	3,001	794.6 (26.5%)
1999/2000 (week 1–7)	116	7.7 (6.6%)	2,530	252.0 (10.0%)
2000/2001 (week 50–9)	141	2.1 (1.5%)	2,327	30.1 (1.3%)
2001/2002 (week 2–6)	69	24.6 (35.7%)	1,608	398.4 (24.8%)
2002/2003 (week 46–4)	96	1.9 (2.0%)	1,837	15.1 (0.8%)
2003/2004 (week 45–49)	55	7.6 (13.8%)	1,252	119.6 (9.6%)
Total	665	79 (11.9%)	12,555	1,610 (12.8%)

Table A10: Number of deaths to pneumonia and influenza predicted by influenza activity in Portugal per influenza-season

Year (influenza period)	50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)
1998/1999 (week 51–5)	67	17.0 (25.4%)	1,348	472.8 (35.1%)
1999/2000 (week 1–7)	50	3.8 (7.6%)	1,195	146.1 (12.2%)
2000/2001 (week 50–9)	60	0.9 (1.5%)	991	16.2 (1.6%)
2001/2002 (week 2–6)	17	11.5 (67.6%)	630	215.6 (34.2%)
2002/2003 (week 46–4)	28	0.9 (3.3%)	772	7.9 (1.0%)
2003/2004 (week 45–49)	14	3.3 (23.3%)	481	65.9 (13.7%)
Total	236	38 (16.1%)	5,417	925 (17.1%)

Table A11: Number of total deaths predicted by influenza activity in Spain per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%
1997/1998 (week 2–6)	301	1.1 (0.4%)	4,414	206.5 (4.7%)	34,881	5131.7 (14.7%
1998/1999 (week 2–10)	508	2.3 (0.4%)	8,026	421.8 (5.3%)	72,128	10746.7 (14.9%
1999/2000 (week 51–5)	384	2.9 (0.7%)	6,144	395.5 (6.4%)	54,004	7555.3 (14.0%
2000/2001 (week 3–13)	528	0.0 (0.0%)	8,199	1.5 (0.0%)	65,350	15.3 (0.0%
2001/2002 (week 1–7)	383	3.8 (1.0%)	5,681	255.3 (4.5%)	52,385	2672.1 (5.1%
2002/2003 (week 4–18)	765	1.7 (0.2%)	11,389	40.2 (0.4%)	93,931	123.3 (0.1%
2003/2004 (week 44–50)	390	2.4 (0.6%)	5,335	155.0 (2.9%)	44,688	742.4 (1.7%
2004/2005 (week 51–5)	388	2.7 (0.7%)	6,201	384.2 (6.2%)	61,515	8520.1 (13.9%
Total	3,647	17 (0.5%)	55,389	1,860 (3.4%)	478,882	35,507 (7.4%

Table A12: Number of deaths to respiratory diseases predicted by influenza activity in Spain per influenza-season

Year (influenza period)	50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)
1997/1998 (week 2–6)	290	79.6 (27.4%)	4,712	1819.4 (38.6%)
1998/1999 (week 2–10)	785	181.5 (23.1%)	13,931	4600.9 (33.0%)
1999/2000 (week 51–5)	499	168.5 (33.8%)	9,965	3150.1 (31.6%)
2000/2001 (week 3–13)	433	0.5 (0.1%)	8,020	5.5 (0.1%)
2001/2002 (week 1–7)	447	99.3 (22.2%)	8,957	1037.7 (11.6%)
2002/2003 (week 4–18)	603	14.4 (2.4%)	12,328	48.3 (0.4%)
2003/2004 (week 44–50)	302	44.1 (14.6%)	6,146	234.3 (3.8%)
2004/2005 (week 51–5)	497	161.0 (32.4%)	11,974	3800.9 (31.7%)
Total	3,856	749 (19.4%)	76,033	14,697 (19.3%)

Table A13: Number of deaths to pneumonia and influenza predicted by influenza activity in Spain per influenza-season

Year (influenza period)	50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)
1997/1998 (week 2 – 6)	55	19.0 (34.5%)	1,110	569.2 (51.3%)
1998/1999 (week 2 – 10)	139	40.6 (29.2%)	3,428	1314.9 (38.4%)
1999/2000 (week 51 – 5)	96	38.0 (39.6%)	2,364	869.5 (36.8%)
2000/2001 (week 3 – 13)	85	0.1 (0.1%)	1,564	1.4 (0.1%)
2001/2002 (week 1 – 7)	94	23.3 (24.8%)	1,895	257.0 (13.6%)
2002/2003 (week 4 – 18)	88	3.1 (3.5%)	2,268	12.0 (0.5%)
2003/2004 (week 44 – 50)	51	9.7 (19.1%)	1,194	56.1 (4.7%)
2004/2005 (week 51 – 5)	92	37.8 (41.1%)	2,723	1075.8 (39.5%)
Total	700	172 (24.6%)	16,546	4,156 (25.1%)

Table A14: Number of hospitalisations to respiratory diseases predicted by influenza activity in the Netherlands per influenza-season

Year (influenza period)	0-19 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
1996/1997 (week 1–7)	13,305	35.3 (0.3%)	2,722	303.8 (11.2%)	6,832	510.3 (7.5%)
1997/1998 (week 4–14)	22,174	26.1 (0.1%)	4,366	46.7 (1.1%)	9,732	296.8 (3.0%)
1998/1999 (week 52–9)	15,900	19.8 (0.1%)	3,830	151.3 (4.0%)	9,313	289.0 (3.1%)
1999/2000 (week 50–4)	11,123	19.4 (0.2%)	2,943	379.4 (12.9%)	7,197	1059.8 (14.7%)
2000/2001 (week 52–8)	14,180	3.5 (0.0%)	3,111	0.0 (0.0%)	6,744	0.0 (0.0%)
2001/2002 (week 5–13)	14,842	20.1 (0.1%)	3,617	66.7 (1.8%)	7,937	8.6 (0.1%)
2002/2003 (week 9–15)	12,013	4.8 (0.0%)	3,032	0.0 (0.0%)	6,272	0.0 (0.0%)
2003/2004 (week 49–1)	7,652	13.4 (0.2%)	1,984	73.8 (3.7%)	4,793	352.2 (7.3%)
2004/2005 (week 4–10)	11,442	18.4 (0.2%)	3,809	244.4 (6.4%)	8,460	886.4 (10.5%)
Total	122,631	161 (0.1%)	29,414	1,266 (4.3%)	67,280	3,403 (5.1%)

Table A15: Number of hospitalisations to pneumonia and influenza predicted by influenza activity in the Netherlands per influenza-season

Year (influenza period)	0-19 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
1996/1997 (week 1–7)	1,087	59.1 (5.4%)	426	57.2 (13.4%)	2,086	167.4 (8.0%)
1997/1998 (week 4–14)	1,528	39.3 (2.6%)	720	10.0 (1.4%)	2,803	97.8 (3.5%)
1998/1999 (week 52–9)	901	29.8 (3.3%)	660	30.8 (4.7%)	2,733	91.8 (3.4%)
1999/2000 (week 50–4)	1,088	46.2 (4.2%)	616	98.8 (16.0%)	2,278	412.1 (18.1%)
2000/2001 (week 52–8)	1,102	5.8 (0.5%)	514	0.0 (0.0%)	2,042	0.0 (0.0%)
2001/2002 (week 5–13)	948	32.6 (3.4%)	676	16.4 (2.4%)	2,503	3.3 (0.1%)
2002/2003 (week 9–15)	689	6.7 (1.0%)	590	0.0 (0.0%)	2,082	0.0 (0.0%)
2003/2004 (week 49–1)	979	36.8 (3.8%)	425	20.7 (4.9%)	1,620	138.2 (8.5%)
2004/2005 (week 4–10)	898	37.1 (4.1%)	757	68.0 (9.0%)	2,926	381.0 (13.0%)
Total	9,220	294 (3.2%)	5,384	302 (5.6%)	21,073	1,292 (6.1%)

Table A16: Number of hospitalisations to respiratory diseases predicted by influenza activity England per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
1997/1998 (week 3–13)	27,168	20.9 (0.1%)	9,664	0.0 (0.0%)	36,130	0.0 (0.0%)
1998/1999 (week 52–8)	26,183	20.7 (0.0%)	12,587	1099.1 (8.7%)	50,563	6225.7 (12.%)
1999/2000 (week 48–2)	30,745	13.7 (0.1%)	12,748	1534.3 (12.0%)	49,750	8849.6 (17.8%)
2000/2001 (week 3–9)	22,402	11.7 (0.0%)	7,881	122.9 (1.6%)	29,578	0.0 (0.0%)
2001/2002 (week 51–3)	18,377	1.2 (0.0%)	6,393	0.0 (0.0%)	25,907	0.0 (0.0%)
2002/2003 (week 2–12)	31,683	3.4 (0.0%)	12,706	0.0 (0.0%)	48,358	0.0 (0.0%)
2003/2004 (week 43–49)	28,179	16.8 (0.1%)	9,550	0.0 (0.0%)	35,675	43.9 (0.1%)
2004/2005 (week 52–11)	41,276	0.7 (0.0%)	17,550	0.0 (0.0%)	65,112	0.0 (0.0%)
2005/2006 (week 1–9)	32,856	8.0 (0.0%)	14,115	0.0 (0.0%)	52,349	0.0 (0.0%)
Total	258,869	97 (0.0%)	103,194	2,756 (2.7%)	393,422	15,119 (3.8%)

Table A17: Number of hospitalisations to pneumonia and influenza predicted by influenza activity in England per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
1996/1997 (week 1–)	2,183	52.8 (2.4%)	1,564	0.0 (0.0%)	8,808	0.0 (0.0%)
1997/1998 (week 4–14)	2,248	42.4 (1.9%)	2,204	246.6 (11.2%)	12,987	1806.2 (13.9%)
1998/1999 (week 52–9)	2,529	28.1 (1.1%)	2,175	358.5 (16.5%)	12,450	2727.1 (21.9%)
1999/2000 (week 50–4)	2,208	29.5 (1.3%)	1,366	28.2 (2.1%)	7,735	0.0 (0.0%)
2000/2001 (week 52–8)	1,606	2.6 (0.2%)	1,187	0.0 (0.0%)	7,194	0.0 (0.0%)
2001/2002 (week 5–13)	2,739	7.9 (0.3%)	2,359	0.0 (0.0%)	12,676	0.0 (0.0%)
2002/2003 (week 9–15)	2,314	34.0 (1.5%)	1,608	0.0 (0.0%)	9,189	13.3 (0.1%)
2003/2004 (week 49–1)	4,568	2.1 (0.0%)	3,592	0.0 (0.0%)	18,325	0.0 (0.0%)
2004/2005 (week 4–10)	3,036	21.7 (0.7%)	2,915	0.0 (0.0%)	15,929	0.0 (0.0%)
Total	23,431	221 (0.9%)	18,970	633 (3.3%)	105,293	4,547 (4.3%)

Table A18: Number of hospitalisations to respiratory diseases predicted by influenza activity in Portugal per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
2000/2001 (week 50–9)	7,318	2.1 (0.0%)	1,723	0.0 (0.0%)	9,996	2.4 (0.0%)
2001/2002 (week 2–6)	4,196	11.2 (0.3%)	1,039	130.0 (12.5%)	6,772	536.4 (7.9%)
2002/2003 (week 46–4)	7,171	2.2 (0.0%)	1,582	0.0 (0.0%)	9,667	0.0 (0.0%)
2003/2004 (week 45–49)	2,768	5.9 (0.2%)	887	51.7 (5.8%)	6,213	162.3 (2.6%)
2004/2005 (week 1–5)	3,583	4.1 (0.1%)	1,103	123.3 (11.2%)	8,613	1109.8 (12.9%)
Total	25,036	26 (0.1%)	6,334	305 (4.8%)	41,261	1,811 (4.4%)

Table A19: Number of hospitalisations to pneumonia and influenza predicted by influenza activity in Portugal per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
2000/2001 (week 50–9)	1,709	14.1 (0.8%)	615	0.0 (0.0%)	4,640	1.4 (0.0%)
2001/2002 (week 2–6)	1,076	68.8 (6.4%)	388	60.6 (15.6%)	3,323	298.5 (9.0%)
2002/2003 (week 46–4)	1,441	11.9 (0.8%)	575	0.0 (0.0%)	4,552	0.0 (0.0%)
2003/2004 (week 45–49)	606	27.4 (4.5%)	346	23.4 (6.8%)	3,034	84.3 (2.8%)
2004/2005 (week 1–5)	759	23.1 (3.0%)	391	52.4 (13.4%)	4,033	595.0 (14.8%)
Total	5,591	145 (2.6%)	2,315	136 (5.9%)	19,582	979 (5.0%)

Table A20: Number of hospitalisations to pneumonia and influenza predicted by influenza activity in Spain per influenza-season

Year (influenza period)	0-14 years		50-64 years		65+ years	
	observed	predicted (%)	observed	predicted (%)	observed	predicted (%)
1997/1998 (week 2–6)	2,533	128.3 (5.1%)	1,131	202.7 (17.9%)	5,888	1222.5 (20.8%)
1998/1999 (week 2–10)	2,591	238.7 (9.2%)	2,286	401.0 (17.5%)	11,673	2523.8 (21.6%)
1999/2000 (week 51–5)	2,370	330.5 (13.9%)	2,221	484.6 (21.8%)	11,215	2090.0 (18.6%)
2000/2001 (week 3–13)	4,062	3.0 (0.1%)	2,148	0.0 (0.0%)	10,590	0.0 (0.0%)
2001/2002 (week 1–7)	3,069	531.7 (17.3%)	2,010	294.5 (14.7%)	10,435	711.0 (6.8%)
2002/2003 (week 4–18)	4,947	229.1 (4.6%)	3,145	0.0 (0.0%)	16,684	1.2 (0.0%)
2003/2004 (week 44–50)	2,896	247.2 (8.5%)	1,568	125.6 (8.0%)	8,176	94.8 (1.2%)
2004/2005 (week 51–5)	2,319	375.9 (16.2%)	2,328	560.1 (24.1%)	15,119	3118.8 (20.6%)
Total	24,787	2,084 (8.4%)	16,837	2,069 (12.3%)	89,780	9,762 (10.9%)

Table A21: Comparison of influenza-attributable hospitalisations and mortality between countries

Country, study	Hospitalisation (rate per 100,000)				Mortality (rate per 100,000)					
	50-64 years		≥ 65 years		50-64 years			≥ 65 years		
	Influenza & pneumonia	Respiratory & circulatory	Influenza & pneumonia	Respiratory & circulatory	Influenza & pneumonia	Respiratory & circulatory	All-cause	Influenza & pneumonia	Respiratory & circulatory	All-cause
Australia [10]	33.3	90.9[b]	157.4	439.5[b]	0.6	2.7[b]	6.4	17.6	91.3[b]	116.4
Hong Kong [19]	-	-	-	-	0.8[e]	7.3[e]	11.8[e]	39.3	102.0	136.1
Italy [3]	-	-	-	-	-	-	-	13.3	-	91.1
Singapore [20]	-	-	-	-	-	-	-	46.9	155.4	167.8
Spain [21]	-	-	-	-	-	-	-	6.4	40.0	57.5
UK[c] [2]	-	19.6[b, d]	-	136.9[b]	-	8.2[d]	-	-	176.6	-
US[a] [11]	37.9	83.8	205.0	445.0	-	-	-	-	-	-
US [9]	-	-	-	-	1.3	7.5	12.5	22.1	98.3	132.5
US [12]	-	-	-	-	-	-	-	18	-	73
Current analysis										
England	0.8	3.6[b]	6.5	21.5[b]	0.5	1.1[b]	2.0	14.1	19.7[b]	33.5
France	-	-	-	-	-	-	1.9	-	-	33.8
Netherlands	1.1	4.6[b]	6.2	16.4[b]	0.2	0.7[b]	2.2	10.3	17.1[b]	45.7
Portugal	1.5	3.3[b]	10.9	20.1[b]	0.3	0.7[b]	1.8	8.6	14.9[b]	42.7
Spain	3.6	-	16.8	-	0.3	1.3[b]	3.2	8.1	25.3[b]	61.1

[a] Primary hospitalisation.
[b] Respiratory only.
[c] England and Wales. Rates are approximated using the 'bacteria included' model.
[d] 45-64 years.
[e] 40-64 years.

Table A22: Comparison of influenza-attributable hospitalisations and mortality between countries: all ages

Country, study	Hospitalisation (% of total hospitalisations)	Mortality (% of total deaths)		
		Influenza & pneumonia	Respiratory & circulatory	All-cause
Czech Republic[a] [22]	-	-	2.6%	2.2%
England and Wales[b] [23]	-	-	-	2.3%
US[b] [9]	-	9.8%	3.1%	2.2%

[a] Circulatory mortality only.
[b] Primary hospitalisations.

Annex 3: ICD codes

Hospital admissions
The impact of influenza on hospital admissions will be estimated from the excess rate of hospitalisation due to influenza by subtracting the average annual hospital admission rate (between October 1st and March 31st) from the hospital admission rate due to influenza during so-called influenza active periods (see further).

Hospital admissions due to influenza are defined as hospital admissions for at least 24 hours and with a discharge diagnosis as shown in box 1.

Operational definitions of hospital admissions and deaths due to influenza

Discharge diagnosis, resp. cause of death
a) Any diagnosis belonging to the ICD chapter Respiratory diseases
b) Influenza and pneumonia (ICD-9: 480-487; ICD-10: J10-J18)
c) Acute bronchitis (ICD-9: 466.0; ICD-10: J20)
d) Acute bronchiolitis (ICD-9: 466.1; ICD-10: J21)
e) Unspecified lower respiratory infection (ICD-9: 490; ICD-10: J 22)
f) Chronic lower respiratory disease (ICD-9: 490-496; ICD-10: J40-47)
g) Bronchitis not specified (ICD-9: 490; ICD-10: J40)
h) Any diagnosis belonging to the chapter Cardiovascular diseases

Hospital admission rates are defined as the number of hospital admissions per 1000 persons of the population at risk. Weekly data (based on the date of discharge) from 11-12 seasons will be included (depending on the availability of 2007 and 2008 data), starting with the 1996-1997 winter season.

Deaths
The impact of influenza on the number of deaths will be estimated from the excess mortality rate due to influenza by subtracting the average annual mortality rate (between October 1st and March 31st) from the mortality rate due to influenza during so-called influenza active periods (see further). For the definition of death due to influenza see box 1.

The cause of death as used in the participating countries' statistics will be applied. Mortality rates are defined as the number of deaths per 1000 of the population at risk. Weekly data (based on the date of discharge) from 14 seasons will be included, starting with the 1993-1994 winter season.