The burden of disease of influenza

Age specific data from the Netherlands, England and Spain

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This project was carried out with funding from Sanofi Pasteur and Sanofi Pasteur-MSD. This report is based on a request made to the European Influenza Surveillance Scheme (EISS) Co-ordination Centre to assess age-specific ILI consultation rates in the Netherlands, England and Spain, paying special attention to children and persons aged 45-64.

Summary

Objective
To calculate the age-specific burden of disease for influenza in three countries (the Netherlands, England and Spain). The results of this analysis might be useful in the decision making to extend routine influenza vaccination to new age groups: infants (0-4 year), children (5-14 year) and adults (45-64 year).

Method
The objective of this descriptive study was met by estimating the excess of physician consultation rates for influenza-like illness (ILI) in eight different age groups ranging from 0 to >74 years during 11 influenza seasons in the Netherlands (1996-2007), 13 influenza seasons in England (1994-2007) and 5 influenza seasons in Spain (2002-2007). The excess was calculated for virus active weeks only and corrected for background ILI consultation rates occurring outside these weeks.

Results
Age groups < 1 year and 1-4 years: only Spain and the Netherlands found evidence for a disproportionately high burden of disease in these age groups. The evidence for Spain was strong, especially for the age group 1-4 years; the evidence for the Netherlands was weak.
Age group 5-14 years: Strong evidence of a relatively high burden of disease for this age group was found in Spain and weak evidence in England.
Age group 45-64 years: None of the countries found good evidence of a relatively higher burden of disease in this age group.

Conclusion
In two out of three countries there is evidence of a disproportionate higher burden of disease for age groups <1, 1-4 and 5-14 years. There is no such evidence for the age group 45-64 years.

Introduction

Burden of disease from influenza

The burden of disease from influenza is two-fold. Firstly, it may cause severe disease and death among the elderly and other vulnerable groups in the population. Excess deaths due to influenza have been estimated to range between 8-44 per 100,000, depending on the severity of the epidemic in a given influenza season. (1, 2). Secondly, the annual large number of mild to moderate cases of influenza are responsible for much absence from work and considerable costs for health and social care services.

Target groups for influenza vaccination

A survey by the European Centre for Disease Control (ECDC) in 2006 on influenza vaccination policy in 23 EU countries found that 17 out of 23 recommended annual vaccination against influenza of persons older than 65 year, two countries in persons over 60 years and one country in persons over 55 years; the remaining 3 countries had issued no recommendation (3). Most countries also recommend vaccination of people over 6 months of age with chronic medical conditions such as chronic heart or lung disease, metabolic or renal disease and immune deficiencies, and of persons living in nursing homes for the disabled.

Few EU countries recommend vaccination of children or pregnant women, which is different from the policy in the United States (4). An expert panel convened by ECDC considered that for children 'there was as yet insufficient evidence on the burden of infection to take any view for or against vaccination' (5).

In the USA routine influenza vaccination has been recommended for the 50-64 years age group since 1999 (4). The rationale for this recommendation was based on the estimation that more than 30% of the subjects in this age group suffer from medical conditions which may lead to higher morbidity and mortality following influenza infection. Currently, such an age based recommendation has not been adopted in Europe.

Efficacy of influenza vaccination

Estimates of vaccine efficacy vary according to the match between vaccine and the circulating viral strain(s), by age group and clinical condition. In clinical trials of inactivated influenza vaccines, vaccination prevented laboratory confirmed illness in 70-90% of healthy adults (6, 7). The reduction in hospitalisations and deaths by vaccination is less dramatic but still significant. However, a flaw in most studies is that the estimates are based on observational studies without virological confirmation and may be biased (8). However, 3 large studies in elderly persons which were controlled for confounding factors reported reductions in risk of hospitalization for pneumonia, ranging from 21-27% and of death from 12-48%. (9, 10).

Aim of the present study

To estimate the age-specific burden of disease for influenza in three countries (the Netherlands, England and Spain). The results of this analysis might be useful in the decision making to extend routine influenza vaccination to new age groups: infants (0-4 year), children (5-14 year) and adults (45-64 year).

Methods

Consultation rates for influenza-like illness (ILI) at sentinel practices in the Netherlands, England and Spain were the backbone of the current investigation.
The phrase consultation rate is used here in accordance with common practice, but the measurement used is of persons with new episodes of ILI and does not include second or subsequent consultations in a particular episode.
Each of the sentinel networks collaborating in EISS (11) has particular characteristics to which we draw attention to as a preliminary to considering the data.

Sentinel Networks: case definitions of Influenza-like Illness (ILI), virological surveillance and vaccination rates

The Netherlands
Network. The Dutch sentinel network known as 'Continuous Morbidity Registration Sentinel Stations The Netherlands' has been in operation since 1970 (12, 13). 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 representative of the total population with regard to age, sex, geographical distribution and level of urbanisation. The sentinel stations report on children in the following age groups: < 1, 1-4, 5-9, 10-14 and in adults in 5 year bands, 15-19… , 80-84, and >84 year. In order to allow comparison with the reports from England and Spain the age groups were consolidated into larger groups : <1 year, 1-4, 5-14, 15-24, 25-44, 45-64, 65-74 and < 74 year. We analyzed data from 21 influenza seasons (1986-2007) in order to study trends in consultation rates. In the comparative study with England and Spain the data of 11 influenza seasons (1996-2007) were analysed, as we had the necessary virological data for this period.
Case definition. The case definition for ILI used by the sentinel GPs is based on the 'Pel criteria' initially described by Pel in 1965 (14). The case definition includes the presence of the following criteria: acute onset of disease, accompanied by a raised rectal temperature of >38C and at least one of the following symptoms: cough, coryza, sore throat, frontal headache, retrosternal pain or myalgia.
Virological surveillance. During winter (weeks 40-20), sentinal 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 preferentially including 1 younger than 10 years, irrespective of severity of symptoms. On average about 20 swabs per week are taken across the network.
Vaccination. A national influenza vaccination programme was implemented in the Netherlands in 1998. Target groups were healthy elderly above 65 years and vulnerable persons with chronic diseases. In 2006 the coverage rate of the elderly was 87% (15). The overall coverage rate increased from 12% in 1995 to 24% in 2006. (In 2007, the Health Council of the Netherlands advised the Minister of Health that influenza vaccination routinely should be offered to healthy persons above the age of 60 years (16)).

England

Network. The Royal College of General Practitioners Weekly Returns Service (WRS) has operated since 1964 (17). In recent years it has included approximately 400 GPs covering 1.1% of the entire population, representative for age, sex socio-economic status and ethnic origin. Historically the GPs reported weekly ('weekly returns') on selected diseases but in recent years on all diagnoses. Data from 13 influenza seasons (1994-2007) have been analyzed, during which the weekly reports were age and gender specific (age groups: < 1, 1-4, 5-14, 15-24, 25-44, 45-64, 65-74 and > 74 years).

Case definition. 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 (18).

Virological surveillance. 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.

Vaccination. Major changes to influenza immunization policy were introduced in 1998 when immunization of the elderly became age related rather than risk related. In elderly persons (65 years and over) uptake increased from 37 % in 1989/90 to 79% in 2005/2006. The overall influenza vaccination coverage rate in Great Britain reached 26% in 2005/2006 (19, 20).

Spain

Network. 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, urbanisation, and some social variables (21). In Spain children between 0-14 year generally consult community paediatricians rather than GPs. Since 1991 GPs and paediatricians participating in SISSS have submitted weekly epidemiological and virological data for age groups 0-4, 5-14, 15-64 and >64 years. From 2002 SISS has been collecting data on a individual basis. The dossier collected on each case includes epidemiological and virological data. In this study data were analysed from influenza seasons 2002-2007 on age groups < 1 year, 1-4, 5-14, 15-24, 25-44, 45-64, 65-74 and < 74 years were analysed.

Case definition. Spain uses the case definition provided by the International Classification of Health Problems in Primary Care (ICHPPC) (14). 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 surveillance. From week 40-20 sentinel physicians are requested to take swabs from nose and throat, on average resulting in about 35 specimens per week for virological determination.

Vaccination. The influenza vaccination rate in elderly persons over 65 years increased from 50.% in 1993 to 70% in 2006 (22,23). The overall vaccination coverage rate of the Spanish population in 2005 was estimated to be 21%. (24).

General methodology

To meet the aim of the current study it was essential that insight was gathered about the burden of disease caused by influenza among the target age groups. Ideally such an analysis should be based on virologically proven cases of influenza, but in practice it can only be based on reported cases of ILI by sentinel networks. To increase the chance that a diagnosis of ILI during an influenza season (running from week 40 of a given year to week 20 of the next year) was caused by influenza rather than other respiratory diseases, two refinements to the analysis were made. Firstly, only the ILI consultation rates occurring in the virus active periods (peak weeks) were taken into account. Peak weeks are defined as those weeks in which 70% of all influenza virus-positive samples are detected in a given influenza season. Secondly, the excess ILI consultation rates occurring in the virus active weeks over the average (background) rate occurring in the remaining winter weeks were calculated (17). See figure A.

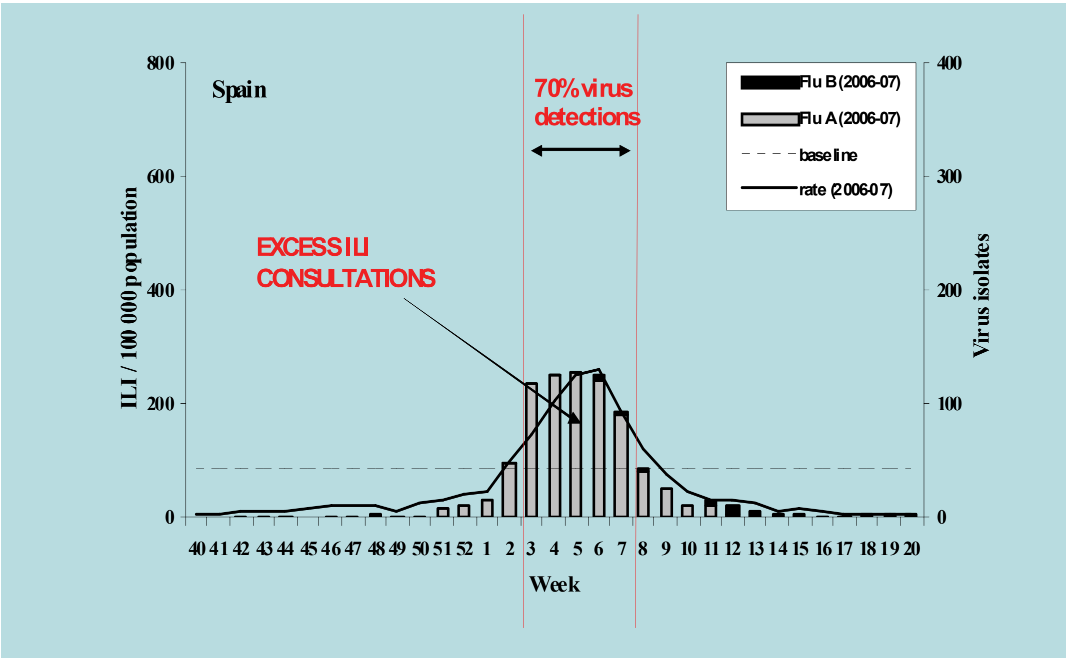


Figure A: Methodology to estimate the excess of ILI consultation rates in virus active weeks. The bars represent the number of influenza virus isolates, the curve represents ILI consultation rates/100,000 in Spain in the 2006-2007 influenza season. In that particular season Spain had 5 virus active weeks. In the results section 'excess' is sometimes presented as 'sum excess' (sum of the excess in all virus active weeks), or as 'average excess' (sum excess divided by number of virus active weeks).

Influenza seasons covered in the present survey per country

The Netherlands

Two different analyses were performed. Firstly, to get an overall picture of trends in ILI consultation rates over time, 21 seasons were included, starting with influenza season 1986-87 and ending with season 2006/2007. In this analysis virological data were not taken into account. Secondly, in concordance with the specific aims and methodology of the current project, excess rates of ILI were examined during 11 seasons for which virological data were available (1996-2007).

England

Data for England were examined over the 13 seasons for which virological were available: 1994/1995 to 2006/2007.

Spain

In Spain only five seasons (2002/2003 – 2006/2007) were included in the current study because before 2002 GPs and paediatricians reported on other age groups than the age groups under investigation in this study.

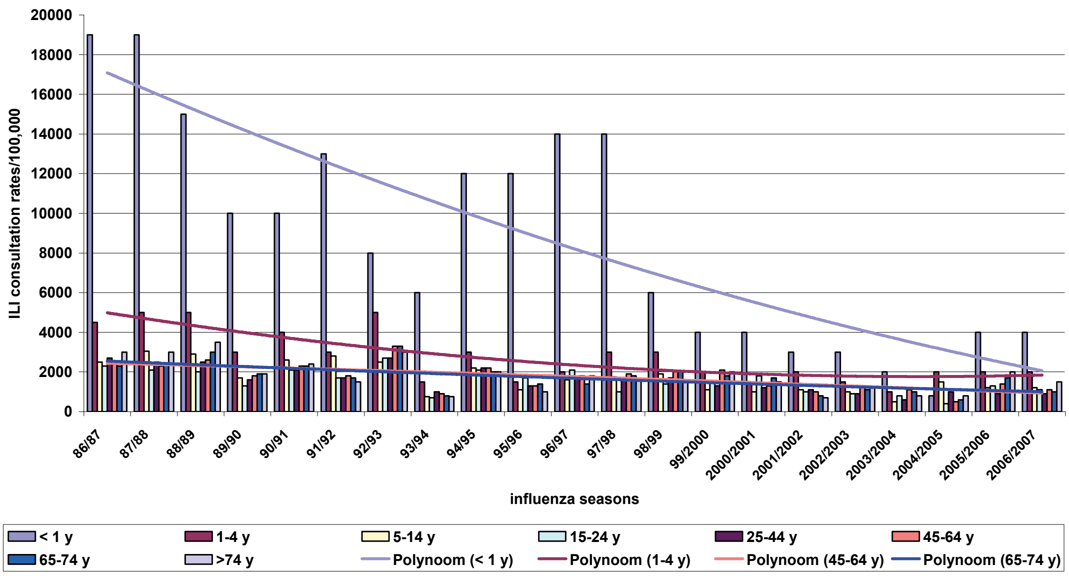
Results

The Netherlands

Trend in ILI consultation rates over 21 Influenza seasons (1986-2007)

The ILI consultation rates in each age group during all winter weeks of 21 seasons are presented in figure 1.

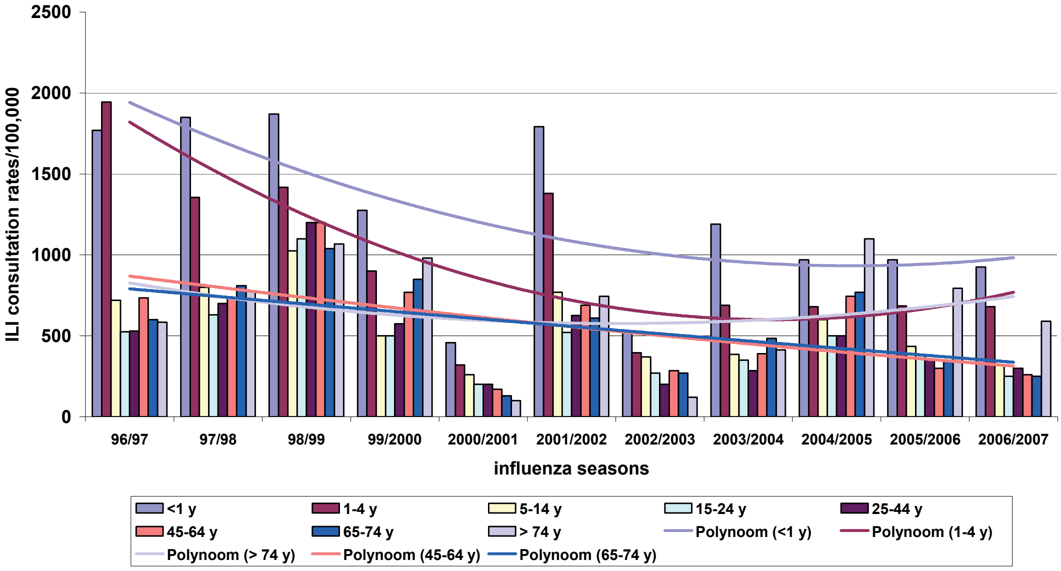
Figure 1: Trends in ILI consultation rates per age group in the Netherlands during influenza seasons 1986-2007



There was a remarkable decrease in consultation rates over time, most notably for the age groups <1 and 1-4 years. For the < 1 year olds the decrease between 1986 and 2007 amounted to > 75%. For the 1-4 year olds the decrease was about 60%. The decrease for all age groups combined was 37%. The trends for the age groups 45-64 and 65-74 years were identical and similar to the all age trend. Although the decrease in ILI consultation rates was most obvious in the age groups <1 and 1-4 years, and especially so between 1986 and 1999, these age groups continued to show the highest ILI incidence rates in subsequent winters.

Trends in ILI consultation rates in virus active weeks over 11 seasons (1996-2007)
Trends in consultation rates during virus active weeks are displayed in figure 2.

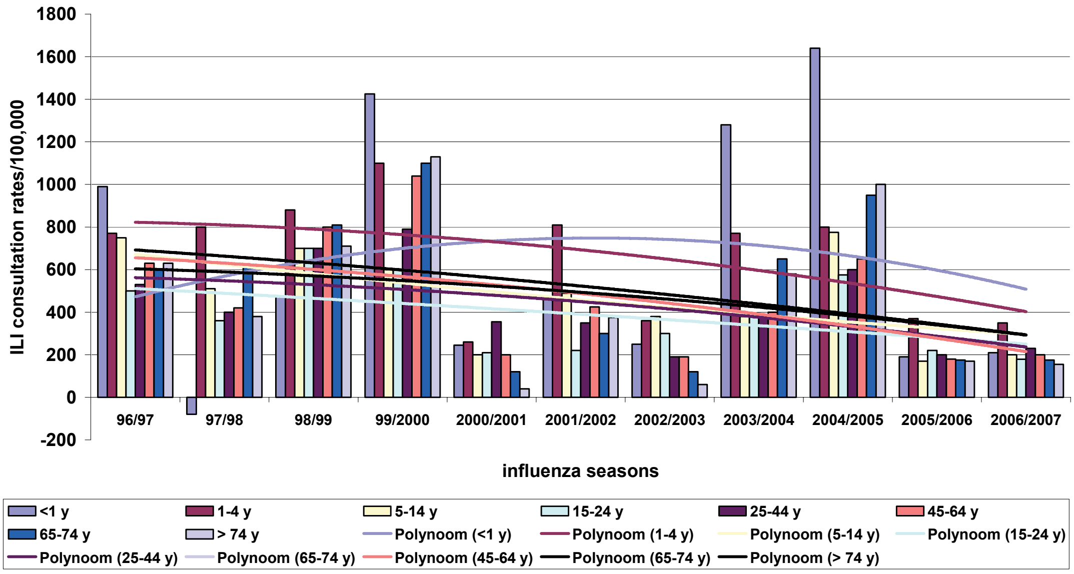
Figure 2: Trends in ILI consultation rates in the Netherlands per age group in virus active weeks during influenza seasons 1996-2007



The trend lines show a steady decrease in consultation rates over time for all age groups except for age groups < 1, 1-4 and >74 years. Trend lines in the first two groups not only are at a higher level during all seasons, but also seem to increase after 2001/2002. After an initial steady decrease the trend line for the > 74 year olds suggests an upward trend in consultation rates from 2001/2002 onwards.

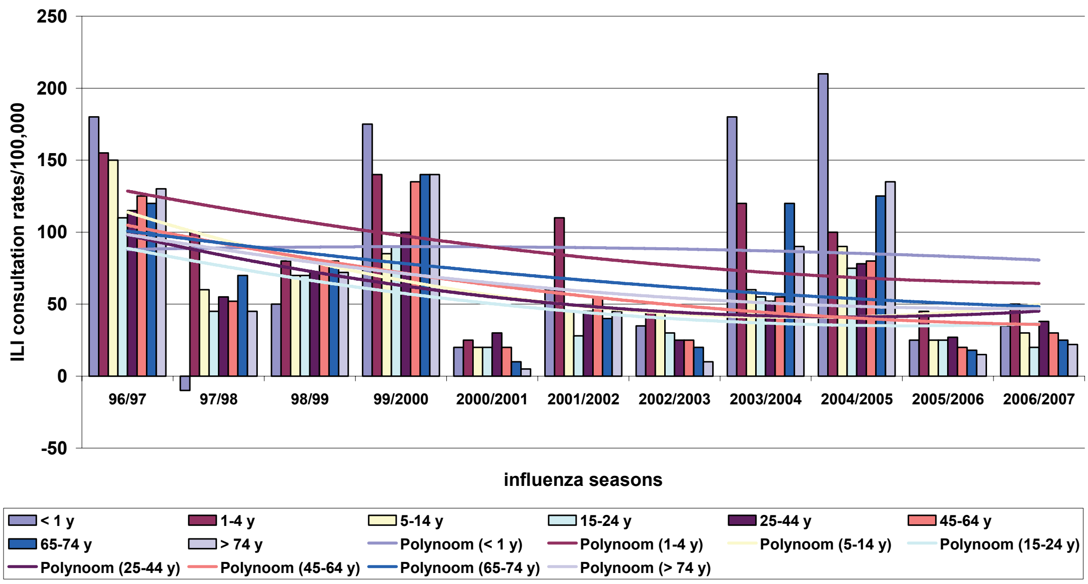
Trends in the excess of ILI consultation rates in virus active weeks over 11 seasons (1996-2007)
Excess consultation rates in virus active weeks are summed and the trends over time are displayed in figure 3.

Figure 3: Sum excess in ILI consultation per age group in the Netherlands in virus active weeks during influenza seasons 1996-2007



The average excess per week is shown in figure 4. Again, the age groups <1 and 1-4 years differ from the other groups by showing the highest cumulative excess and average excess. The difference between the age group 1-4 years and the trend for all ages combined is statistically significant (Wilcoxon signed rank test p = 0.004). The trend observed for the > 74 year olds in the previous paragraph, has disappeared: this trend is now similar to the other age groups.

Figure 4: Average excess in ILI consultation rates per age group in the Netherlands in virus active weeks during influenza seasons 1996-2007



Conclusions for the Netherlands

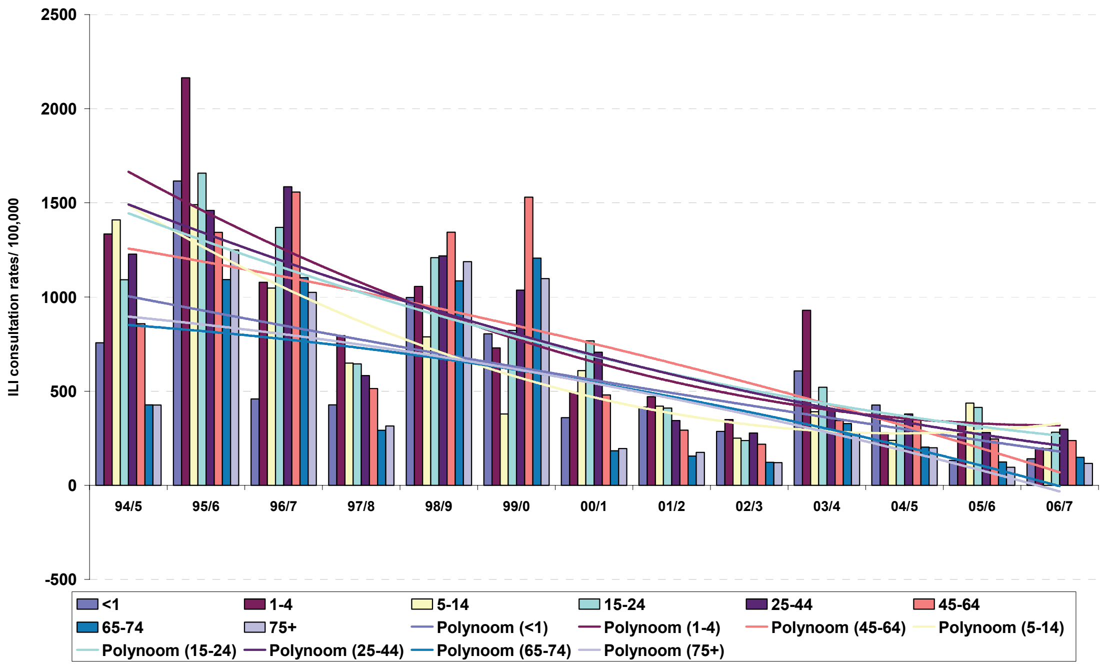
1. Between 1986 and 2007, a remarkable decrease in ILI consultation rates during the influenza season has occurred, especially for the age groups < 1 and 1-4 years.
2. Analyses restricted to virus active weeks in influenza seasons 1996-2007 showed that most of these apparent differences between age groups were no longer evident, except for the age groups < 1 and 1-4 years, which continued to show the highest consultation rates.
3. We found no indication that burden of disease for influenza in age group 45-64 years differed from other adult age groups.

England

Trends in ILI consultation rates in virus active weeks (1994-2007)

The results are depicted in figure 5. Also in England a declining trend in ILI consultation rates for all age groups occurred. Between 1994 and 2007 the decrease in ILI consultations during virus active weeks amounted to about 65%.

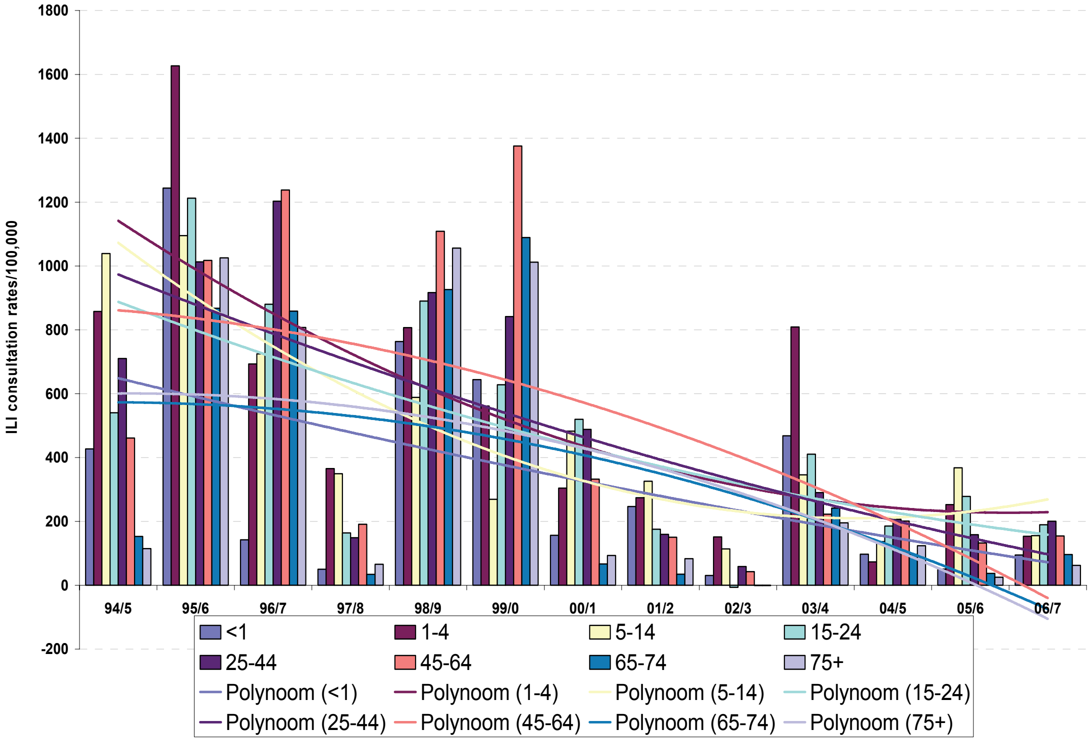
Figure 5: Trends in ILI consultation rates per age group in England in virus active weeks during influenza seasons 1994-2007



Trend lines in the age groups < 1, 65-74 and < 74 years are lower than in other age groups. Rates of ILI in the age groups between 1-64 years are higher than those at the ends of the age range, reflecting the comparative underdiagnosis of ILI in these age groups.

Trends in the excess of ILI consultation rates in virus active weeks (1994-2007)
The results are given in figures 6 and 7. The picture emerging from the previous paragraph remains the same, although less striking; the very young and the elderly age groups generally have the lowest excess in ILI consultation rates as compared to the other age groups. The trend line in figure 7, in which the average excess in ILI consultation rates is depicted, suggests that the age group 45-64 years exhibits the highest consultation rates, although it is obvious that the differences between groups are small.

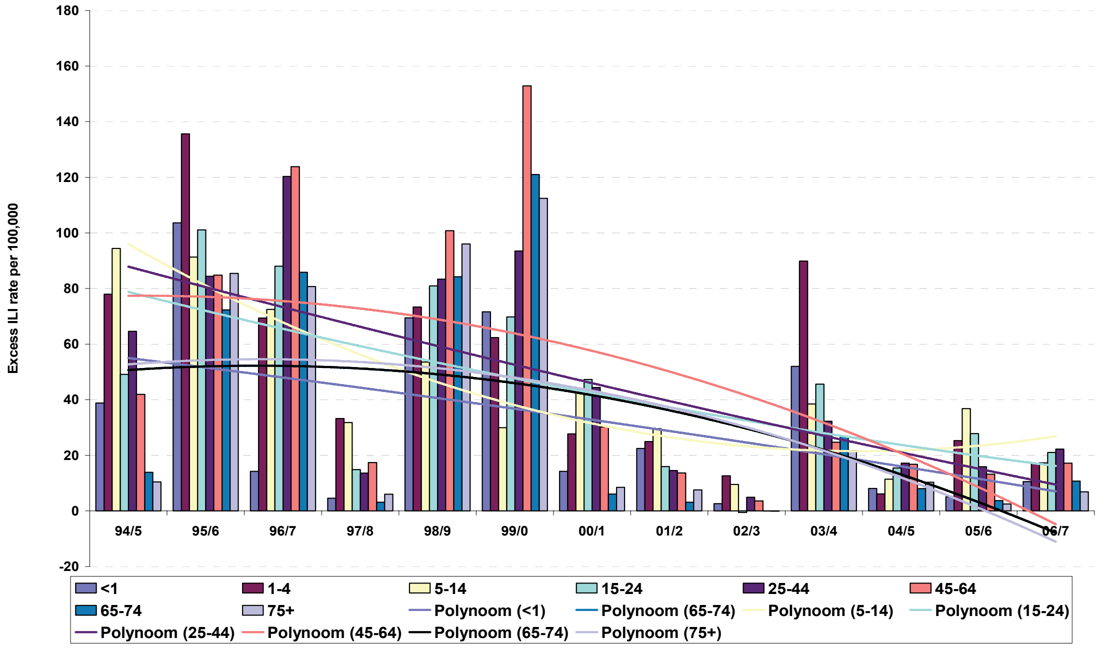
Figure 6: Sum excess in ILI consultation rates per age group in England in virus active weeks during influenza seasons 1994-2007



Conclusions for England

1. Between 1994 and 2007 the ILI consultation rates during virus active weeks decreased about 65%.
2. Age groups < 1, 65-74 and < 74 years show the lowest excess in ILI consultation rates, age group 45-64 the highest.

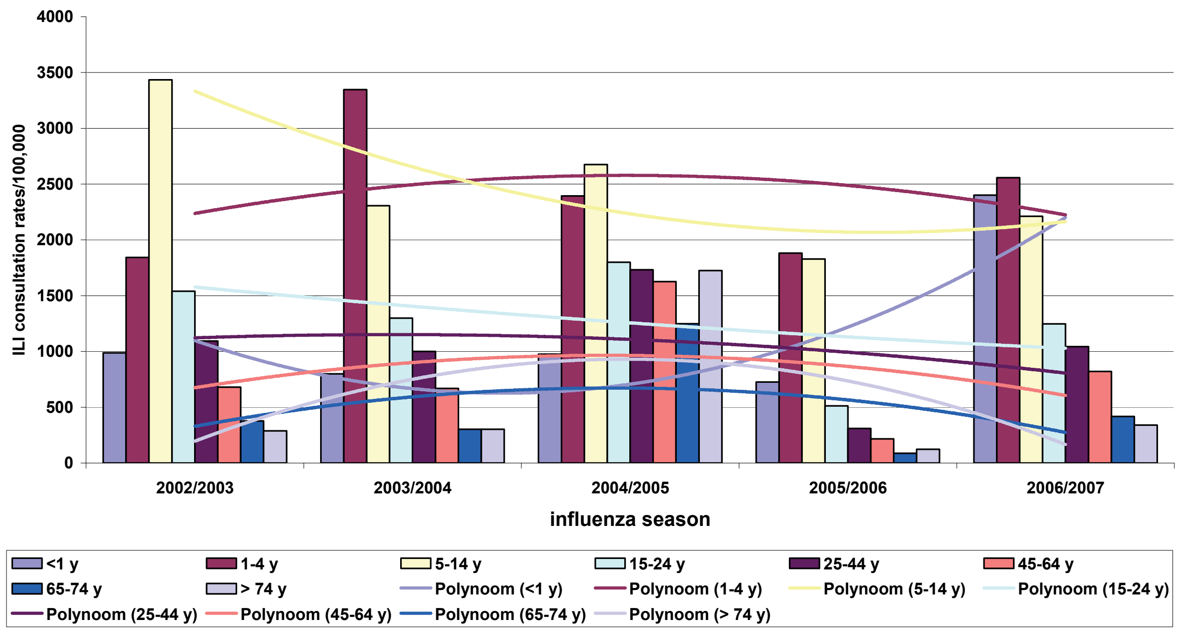
Figure 7: Average excess in ILI consultation rates per age group in England in virus active weeks during influenza seasons 1994-2007



Spain

Trends in ILI consultation rates in virus active weeks (2002-2007)

Figure 8: Trends in ILI consultation rates per age group in Spain in virus active weeks during influenza seasons 2002-2007



Between 2002 and 2007 no clear changes in overall and age-specific ILI consultation rates were evident (figure 8). This is not different from the results in the Netherlands and England because the decreasing trends observed for those countries occurred for a great deal before 2000.
The most remarkable finding for Spain is the consistently high consultation rate for the age groups 1-4 and 5-14 years. By contrast, the excess in ILI consultation rates in the age groups 65-74 and > 74 year are remarkably low (figures 9 and 10).

Figure 9: Sum excess in ILI consultation rates per age group in Spain in virus active weeks during influenza seasons 2002-2007

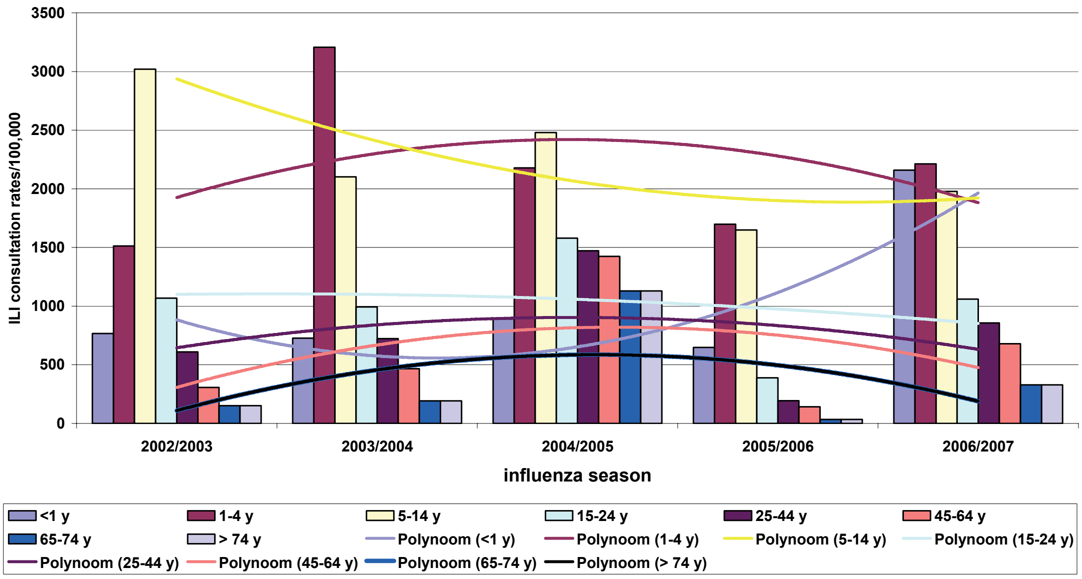
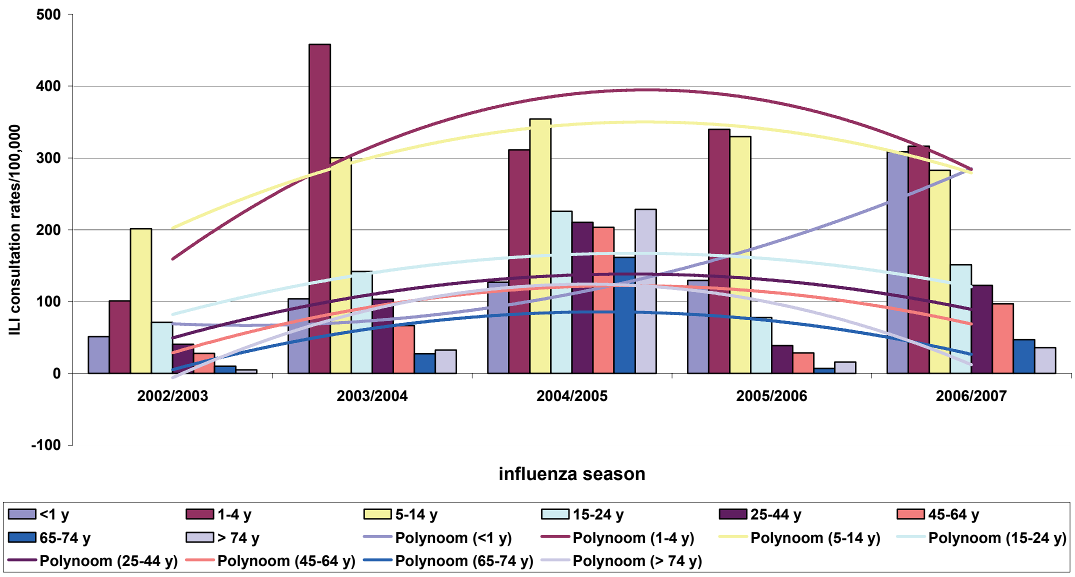


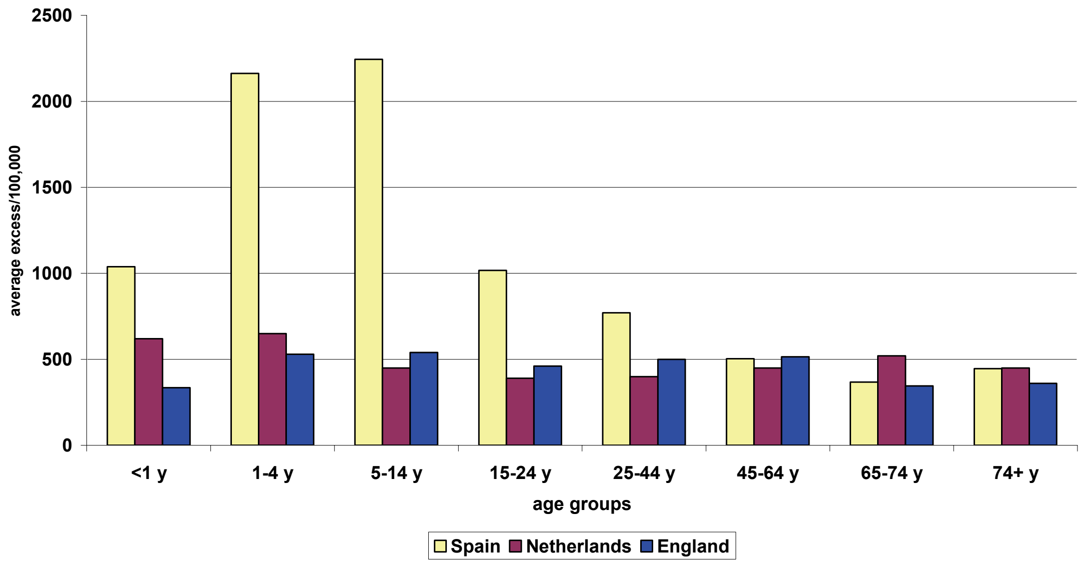
Figure 10: Average excess in ILI consultation rates per age group in Spain in virus active weeks during influenza seasons 2002-2007



Conclusions for Spain
The most remarkable finding for Spain is the consistently high consultation rate for the age groups 1-4 and 5-14 years. By contrast, the excess in ILI consultation rates in the age groups 65-74 and > 74 year are relatively low, except for season 2004-2005, in which ILI consultation rates were considerably higher than in the other seasons.

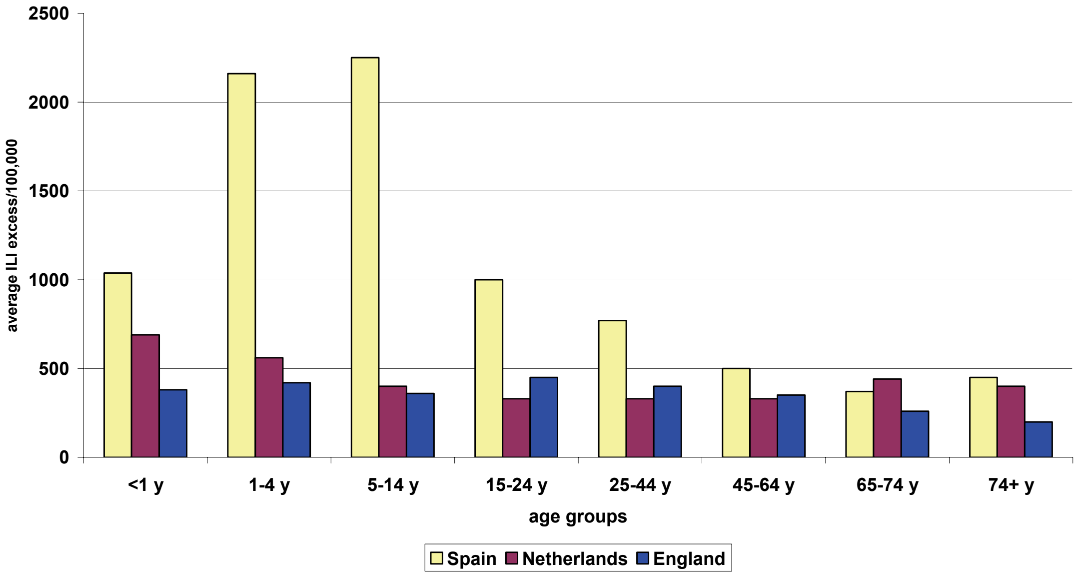
Comparison between Spain, the Netherlands and England
To obtain an overall picture of the results described in the previous paragraphs the mean age dependent sum excess rates per country were calculated and plotted in 2 comprehensive graphs (figures 11 and 12). In figure 11 all influenza seasons years were included: 11 for the Netherlands, 13 for England and 5 seasons for Spain.

Figure 11: Mean ILI sum excess per age group in virus active weeks calculated for 5 influenza seasons in Spain (2002-2007), 11 in the Netherlands (1996-2007) and 13 in England (1994-2007)



In figure 12 only the mean sum excess rates of the 5 overlapping seasons 2002-2007 are depicted.
From both figures it can be appreciated that the most remarkable results are those from Spain where the mean sum excess rates for the age groups <1, 1-4, 5-14 and 15-24 years are 2-3 times higher than their equivalents in the Netherlands and England, especially the age groups 1-4 years and 5-14 years show exceptionally high rates. For the latter 2 age groups the odds ratio for Spain (versus Netherlands + England combined) is 2.8; 95% CI 2.6-3.1.

Figure 12: Mean ILI sum excess per age group in virus active weeks calculated for 5 influenza seasons (2002-2007) in Spain, the Netherlands and England



The second conclusion concerns the similarity of excess rates calculated for the Netherlands and England. The differences between the two countries are small and, if anything, seem to indicate that in the Netherlands the highest excess rates were found for the age groups < 1 year and 1-4 years and 65-74 years, whereas for England the highest excess rates occurred in the age groups 5-14, 15-24, 25-44 and 45-64 years. The results from the Netherlands in the age groups < 1 year and 1-4 years, although less excessive, are generally in agreement with those of Spain.

The third conclusion concerns the overall similarity in the three networks of the excess rates in the age groups 45-64, 65-74 and >74 years.

General conclusions and discussion

The objective of the present study was to investigate the age-specific burden of disease for influenza and to explore whether there might be a basis for extending routine annual influenza vaccination to children < 1 year olds, 1-4 year olds, 5-14 year olds; and adults between 45 and 64 years. The objective was met by estimating the excess of ILI consultation rates for eight different age groups in the Netherlands, England and Spain during 11, 13 and 5 influenza seasons respectively, irrespective of the dominant virus in a given season.

The following conclusions can be drawn:
1 Age groups < 1 year and 1-4 years
Only Spain and the Netherlands found evidence for a relatively high burden of disease in these age groups. The evidence for Spain was especially strong for the age group 1-4 years, the evidence for the Netherlands was weak.
2 Age group 5-14 years
Strong evidence of a relatively high burden of disease for this age group was found in Spain and weak evidence was found in England.
3 Age group 45-64 years
None of the countries found good evidence of a relatively higher burden of disease in this age group.

For a balanced appreciation of the present results it should be kept in mind that they are based on clinical incidence rates of ILI and not on virologically confirmed cases of influenza. In routine practice GPs diagnose ILI in a “loose” fashion based mainly on clinical experience and the month of the year rather than on strict criteria. Because the delay between symptom onset and consultation with a GP is highly variable, the diagnosis is more dependent on the reported symptoms than on objective findings observed by the doctor at the time of presentation. To circumvent this problem of misdiagnosis as much as possible we therefore only used the ILI consultation rates from weeks in which a high proportion of seasonal influenza virus was detected, and calculated the excess in these so-called virus active weeks. This increases the likelihood that a diagnosis of ILI is due to influenza, provided other viruses are not circulating at the same time.

A particular difficulty of estimating the impact of ILI in virus active weeks is the recognition that infection with RSV may mimic or underlie infection with influenza virus, especially in young children and elderly (25). Estimating of the differential impact of influenza and RSV presents therefore problems because both viruses often co-circulate in mid-winter periods and it is not common practice to investigate patients routinely for both viruses (26).

From the methodological viewpoint we also need to recognize that the impact and burden of influenza is also seen in clinical syndromes other than ILI and this is particularly so for acute otitis media and acute bronchitis in children and for acute bronchitis in the elderly.

To make matters even more complicated, the current results are based on data obtained in three different European countries with differences in the organization of primary care and probably in the attitudes of the public towards health care utilisation. Particularly germane to the present study Spanish children under 14 years of age consult a paediatrician rather than a GP, although the organization of the Primary Health Care System in Spain ensures similar access to paediatricians and GP. In Spain there were particularly high excess of ILI consultation rates in children, which were much less apparent in the Netherlands and England.

The results from Spain cover a shorter period than those from the Netherlands and England but contribute more to the overall conclusions of the present study. Is the high excess rate of the 0-14 year olds in Spain a reality or an artefact? A strong argument that the excess is real and not paediatrician-driven is the finding that in Spain also the age groups 15-24 years and 25-44 years who consult a GP show high excess in ILI consultation rates.

There are other reasons that may explain the differences between Spain and the Netherlands/England. It is possible that in Spain the higher consultation rates for ILI are a reflection of a different public attitude towards the use of primary care in general. Support for this notion is presented in table 1. It is clear that the general attitude towards the use of primary care in Spain indeed is different. Between 1997 and 2005 the yearly outpatient contacts per person ranged from 8.2-9.5 in Spain versus 5.3-5.9 in the Netherlands and 5.4 in the United Kingdom (27).

Table 1: Contacts for primary care per person per year

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005
Netherlands	5.9	5.7	5.8	5.9	5.8	5.6	5.5	5.3	5.4
UK		5.4							
Spain	8.2				8.7		9.5		
EU	6.8	6.7	6.7	6.7	6.7	6.8	6.9	6.8	6.8

Influenza may have had a greater impact in the limited number of seasons studied in Spain. In this regard the mix of influenza A H3, A H1 and B epidemics would be particularly significant in children. The virulence of influenza may change as it progresses through Europe and in recent winters there has been a suggestion of a South-North spread (28). The duration of the epidemic period as measured in the number of active weeks influences the estimate made by this method. A very long period of activity is usually indicative of a minor epidemic and gives maximum potential for confusion from other viruses. It is noteworthy that in the season 2002/2003 Spain experienced a particular long influenza period (table 2).

Table 2: Number of virus active weeks in the Netherlands, England and Spain during 5 influenza seasons

Influenza season	The Netherlands	England	Spain
2002/2003	5	8	15
2003/2004	5	6	7
2004/2005	6	8	7
2005/2006	6	7	5
2006/2007	7	6	7

Final remarks

Was their evidence for a higher burden of disease in certain age groups? Yes, some evidence for a higher burden of disease, likely caused by influenza, was observed for infants and children up to the age of 14 years. However, as we did (and could) not define strict criteria for ’evidence’ at the start of this study, the current results should be interpreted with caution.

Real evidence that certain age groups may suffer more from the impact of influenza than others should come from a follow-up study that addresses the excess in hospitalization and mortality during virus active weeks. This follow-up study, which also will be performed for the Netherlands, England and Spain, is currently being designed.

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Organisation of EISS

Countries in Europe have shared detailed clinical and virological data via the European Influenza Surveillance Scheme (EISS) since 1996. This collaborative project is partially funded by the European Commission through the European Centre of Disease Prevention and Control (ECDC) and currently includes 30 countries. The scheme covers a total population of about 450 million inhabitants and an area of roughly 12 million square kilometres. EISS collects two types of data on influenza activity each season: 1) clinical and virological data collected by sentinel GPs and 2) virological data from non-sentinel sources.

The assessment of influenza activity is largely based on data reported by sentinel GPs. The GPs report clinical cases of influenza-like illness (ILI) and/or acute respiratory infection (ARI) to a central registry and take respiratory specimens that are sent to a national reference laboratory for testing. This ensures that the clinical data reported by the sentinel physicians are validated by virological data on influenza.

The national reference laboratories also report laboratory test results on non-sentinel respiratory specimens e.g. specimens from hospitals or non-sentinel physicians. The national reference laboratories participate in the 'Community Network of Reference Laboratories for Human Influenza in Europe' (CNRL), which is coordinated by EISS. CNRL works closely with the WHO through its network of National Influenza Centres and collaborates with the Centre for Reference and Research on Influenza at Mill Hill, London, UK.