euroMOMO

European monitoring of excess mortality for public health action

Work Package 6 Report

Understanding crude mortality: learning from retrospective data

2011

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1. Introduction & summary

We present the analyses conducted by Work Package 6 which is about 'Understanding mortality time-series' in Europe. This work package is part of the project: European Monitoring of Excess Mortality for Public Health Action (EURO-MOMO).

This work package had the following two objectives:

1) To describe and analyse rapid changes and trends in historical crude mortality data in different European settings (country specific results).

> We present results from 5 countries which performed retrospective analyses on their mortality data: Sweden, Denmark, The Netherlands, U.K and Finland. All countries explored how mortality trends are affected by trends in other factors. These factors could include various commong infections (such as influenza A) and extreme temperature.
>
> What our results reflect is that there is no uniform 1) method, 2) data (available variables) or 3) general historical circumstances (regarding: public health factors, pathogen circulation, climate, or other major events) that currently allow for performing uniform extensive *multivariable* retrospective analyses across European countries. The presented country- and method-specific results help give insight in mortality trends in specific countries and the factors which are of influence on these trends in specific countries. Different combinations of factors are studied per country, but influenza is the infection which currently is included in most studies, although the measure of it's circulation varies across studies (from lab detection data, to morbidity/ILI indicators). Further research on the impact of all possible infection and environmental factors on overall mortality (and how they possibly interact) is necessary in gaining further understanding of both historical mortality trends and of detections of excess from real-time mortality-monitoring systems in European countries.

2) To explore the added value of pooling data on excess mortality so as to describe mortality changes & trends across several European countries combined.

In essence these analyses showed that pooled analyses are possible and that both country-specific and pooled analyses are important:

> To include as many countries as possible, pooled analyses are performed on overall mortality numbers without the inclusion of co-factor data, except for age. Also the EuroMOMO hub has to take responsibility for only publishing country specific z-scores instead of detailed original data. For the pooled analyses to be a useful tool in public heath surveillance it is important that as many countries as possible participate, and they participate every week.
>
> It is important that the pooled analyses are interpreted in combination with country specific analyses. Therefore we recommend showing the polled z-score supplemented with the country specific z-scores.

Pooled analyses can reveal changes in number of deaths that would have been unnoticed in the separate country analyses. Hence, timely pooled analyses can be a valuable tool in public health surveillance, especially for smaller or vulnerable groups like infants and young children or women in the fertile age.

2. Understanding mortality time-series: Country-specific cases

2.1. Mortality in Sweden

2.1.1. Causes of annual mortality variation in Sweden: effects of Influenza A, Influenza B, RSV and extreme temperature. (Bernadette Gergonne et al).

Causes of annual mortality variation in Sweden:

effects of Influenza A, Influenza B, RSV and extreme temperature.

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Introduction

Measuring the contribution of environmental factors to excess mortality is essential to evaluate the severity of public health events and improve public health interventions.
Influenza(1), extreme cold (2,3), extreme heat (4) and air pollution (5-7) are recognized as factors contributing to an excess of deaths in a population, directly or by triggering or increasing the severity of other conditions, prematurely leading to death.
In Sweden, the variety of climates and age group distributions of the population from North to South is likely to lead to different exposure and susceptibility to the various factors possibly contributing to excess of deaths. An in-depth analysis accounting for geographical variation in climate, virus spread and age distribution may therefore contribute to a better understanding of factors leading to an excess of deaths. For that purpose, we designed a multivariable regression model and applied it to historical time series of mortality aggregated by week. The model was used to test the following hypotheses:
- Hypothesis 1: Influenza A/H3, A/H1, A/H1N1-2009, influenza B, RSV, extreme cold and extreme heat contribute to unexpected mortality peaks in Sweden.
- Hypothesis 2: There are regional differences
- Hypothesis 3: There are age group differences

Methods

Data sources

Only data that was easily available on a weekly basis, at both national and at regional level was used to compute the model. In Sweden, the Tax Agency is responsible for the Swedish Population Register and compiles weekly updates of mortality individual records. Mortality data from the beginning of 2001 to February 2010 was obtained. The Swedish Institute for Infectious Disease Control (SMI) provided the weekly number of laboratory confirmed influenza and RSV cases, identified and reported by the National reference laboratories in each county. The daily meteorological data were retrieved from the World Data Center for Meteotology (8). In each of the 21 Swedish Counties, one meteorological station was chosen to be the closest to the main city.

Individual mortality data were aggregated by week of death occurrence (from Monday to Sunday) for Sweden, by age group (below one year, 1 14, 15 to 44, 45 to 64, 65 to 74, 75 to 84 and above 84 years), and for the North, East and South regions of Sweden (as defined by the Nomenclature of Territorial Units for Statistics level 1 (NUTS 1) (9).

A Serfling like method was applied to model the expected baseline mortality (REF simonsen viboud…). A generalized linear model (glm) of the Poisson family was fitted on the weeks without extreme temperature and less than 5 influenza A isolations in the area studied in order to captures cyclical seasonality. The expected baseline was subtracted from the mortality time series to compute a de-seasonalised working time series. Influenza B and RSV weekly number of isolations were introduced in the model. To account for the yearly variations in influenza A strains, 3 variables were computed distinguishing weekly number of influenza A isolation during seasons with a large predominance of H3, seasons with a comparable mix of H1 and H3 and seasons with predominant H1. The weekly average temperature and its baseline (trend + sine term) were computed for each area. Extreme cold and heat were defined by temperature variations below the lowest and above the highest level of the baseline temperature. Only extreme heat and extreme cold temperature indicator were entered separately in the multivariable model of de-seasonalised mortality as an additive terms.
De-seasonalised mortality was modelled using a generalized linear model of the Poisson family with an identity link, on the available data sets, week 2001-27 to 2010-8. Remaining autocorrelation was controlled in the final model (10,11). The decision to remove or maintain a variable in the final model was based on its statistical significance for each of the series tested, and also on the visual examination of its impact on the series variation and on the coherence of the results between series.

An excess of deaths was defined as the difference between the observed and the expected baseline mortality. Annual excess of deaths were computed for each series by aggregating weekly number of deaths from week 27 to week 26 each year (instead of 1 to 52) in order to capture the whole winter season, and the whole summer season (from July). Crude and specific mortality rates were computed using the Swedish population by age group, average over the study period. Direct age-standardized mortality rates were computed, using the European-Scandinavian reference population (12), covering 8 years from week 27 2001 to week 26 2009.
In order to also assess and compare the amplitude of excess mortality in the various population subgroups, standardization using Z-scores were also computed, after a 2/3 power transformation used to normalize the series(13). For comparability with other studies, excess of death was also expressed as a proportion of the expected mortality. Excess related to extreme cold and heat was expressed as the percentage of increase for one Celsius degree variation. Time series and results graphs were finally re-composed to display cyclical seasonality and the various components computed by the model.

Results

Swedish population

The average population of Sweden during the Study period was 9.10 million. The East of Sweden has the youngest population with only 16 % above 64 years, compared to 18% in the South and 19% in the North (Table 1). Around 90,000 deaths are expected every year in Sweden (crude mortality rate: 10/1000/year, age-standardized mortality rate: 5.6/1000/year). An average of around 2000 deaths is considered in excess each year (2.2 % of the annual mortality). Graphs displaying the results of the final model (Figure 1), suggest that cyclical baseline is a good predictor of mortality in the absence of influenza and extreme temperatures and, in parallel that influenza and extreme temperature explain most of the variations of mortality above the expected.

Seasonal influenza A

Influenza A represent between around 200 and 2600 excess deaths per year according to the amplitude of the seasonal influenza epidemic (Table 3, Figure 1). In the 3 regions, Influenza A was significantly associated with an increased mortality without significant differences between regions (Figure 2 - c). Over the study period, results suggest that influenza increased mortality by around 1.2 %. The risk of dying from influenza A significantly increased from 45 years of age (Figure 3-b) but also between 1 to14 years. In that age group, an average excess of 7 deaths per year is observed, varying between 1 to 17 deaths according to the importance of the influenza season (expected mean: 3.5 death per week, Standard Deviation: = 5.5).

Influenza A H1N1-2009

Influenza A/2009-H1N1 was significantly associated with an increased number of deaths only in children from 1 to 14, visible 2 weeks before the peak of laboratory confirmation (excess: 17 [4-39], corresponding Z-score 0.38, p = 0.01). Visually, the peak was identifiable in the 3 region of Sweden, but not statistically significant (Figure 4).

Influenza B

Influenza B was not significantly and consistently associated with an increased number of deaths nor could it visually explain any single peaks or shift in the various series. That variable was removed from the final model.

RSV

Impact of RSV was statistically significant only in children between 1 and 14 years in the region East and North and at National level (according to the model, an average of 8 to 9 deaths per year in excess above the 171 annual deaths expected). When studying the graphs of the time series, this did not correspond to any identifiable peaks or sustained shifts above the cyclical seasonality. No impact at all could be identified in the South of Sweden or any of the other age groups (inconsistency of the direction of the effect, very broad confidence interval crossing 0 and very low significance level). Therefore it was considered that results observed in the East and North of Sweden were related to a random phenomenon or a very small uncontrolled cyclical seasonality. RSV was removed from the final model.

Extreme cold

Extreme cold corresponded to averaged weekly maximal temperature below respectively -2.7, -0.4 and 1.75 °C for the North, East and South region of Sweden. The best fit was obtained without time lag. During the winter 2009-2010, around 1200 deaths were attributed to extreme cold (Table 3). Only the mortality above 45 years significantly increased with extreme cold conditions and

population above 75 years is mostly affected (Figure 2). The impact of one Celcius degree decrease declined with the latitude (Table 4) and was significantly larger in the South and in the population above 65 years (Table 4, Figure 2).

Extreme heat

Extreme heat corresponded to averaged weekly maximal temperature above respectively 21.2, 23.1 and 22.5 °C for the North, East and South region of Sweden Extreme heat significantly increased mortality at national level, in the South and East of Sweden. The risk of dying associated to extreme heat was 2.1 / 100,000 / year on average, at National level. Between 87 and 362 deaths were attributed each year to the effect of heat. The impact of one Celsius degree increase also declined with the latitude (Figure 4).

Unexplained peaks

Several mortality peaks were not explained by the model. Those unexplained peaks are generally visible and concomitant in all regions and frequently occur during the last weeks of each year, with a large variability of amplitude every year. These peaks seem more important in the North of Sweden, compared to the other regions and concern mainly the elderly > 75 (data not shown). We must notice that the peak occurring in late 2004 is partly, but not only, related to the effect of the Tsunami on Swedish tourists visiting Thailand (around 600 deaths during the week 52 of 2004).

Discussion

Methodological choices

Our method slightly differs from previous studies focused on respiratory pathogens by also adjusting on and studying the effect of extreme temperature in a multivariable regression model applied on de-seasonalised time series. Crude, age and Z-score standardised indicators facilitate interpretation and comparison of unexpected variation between different populations.

Regression methods are commonly used to study the impact of respiratory viruses on mortality (14,15), but confusion possibly induced by cold weather is rarely controlled or the respective impact of pathogens and temperature rarely compared. Removing cyclical seasonality when studying times series is highly recommended (10,11), but rarely applied in previous similar researches. To control the cyclical seasonality in American mortality series, Thomson et al. introduced a 52 week sine cycle in their regression model. However, the risk of finding erroneous correlation persists if other explanatory variables are also annually cyclical. In such a case, a statistical link with mortality cannot be interpreted and the possible partial contribution to the cyclical part of mortality can not be accurately computed.

The use of age standardisation is a widely recommended approach (12) but is rarely applied in studies comparing excess of death attributed to influenza, heat and cold between different cities or countries which may impair interpretation of the results. Comparing excess rate (reported to the population size) does not inform about the importance of the excess compared to the baseline and expressing an excess as a proportion of the baseline will overestimate its importance in series with small number of deaths, as visible Figure 3b. An increase of mortality is statistically significant if its corresponding Z-score crosses 1.96 (for an alpha risk of 5%). The respective amplitude of excesses measured in 2 different populations can be compared using Z-scores and will be statistically different if the confidence intervals of their respective Z-score do not overlap. Crude, age and Z-score standardised indicator of excess mortality should be examined together in order to really appraise the pattern of variations, facilitate comparisons.

Our method is robust and easy to apply but present some limitations. Pollution was not included in the model. Weekly variation in the average of maximal temperature can reflect one single very warm or cold day as well as several days with a moderate increase. In addition, the number of laboratory isolations was not large enough to enable a breakdown by age group but only by region. Using the total number of isolations for modelling mortality of each age group implies that virus transmission is similar in time and amplitude among age groups, which may not be true.

Excess of death attributed to respiratory viruses and extreme temperature.

As expected, seasonal influenza seems to mostly increase mortality in population above 45 years of age, and the amplitude of the effect is similar to previous studies (14,16-18) . The results also suggest that the impact on the mortality of the 1 to 14 years children is significant and takes visually the form of a sustained but very small increase of mortality over several weeks. However, it concerns a very small number of children. Impact of seasonal influenza in that specific age group has rarely been scrutinized before. Alike the elderly, Influenza may increase mortality of young patients with severe co-morbidities but may not always be diagnose as a cause of deaths.
Results suggest a possible effect of influenza A/H1N1-2009, visible only from 1 to 14 years, 2 weeks before the peak of laboratory confirmations, but concomitant to the peak of ILI (week 45-46). Its amplitude is comparable to the excess observed during the 2004-2005 influenza epidemic (a specific mortality rate of 1.1/100,000).
In our study, RSV does not explain mortality peaks above the cyclical baseline. RSV certainly contributes to mortality but its cyclical pattern makes its real contribution to mortality very difficult to disentangle using regression method and may lead to large bias. The impact of extreme cold is substantial and some years, comparable, to the impact of influenza. Unexplained peaks of mortality should be investigated further.

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Tables and Graphs

Table 1: Distribution by age group of the Swedish population by regions and European reference population. Map of Sweden, the 3 regions (NUTS 1) and 21 counties.

Age group	WHO European Reference population	Sweden	South	East	North
Under 1 year	1.6	1.0	1.0	1.1	0.8
1 to 14 years	20.4	16.1	16.0	16.5	15.2
15 to 44 years	42.0	39.3	39.1	40.9	36.6
45 to 64 years	25.0	26.0	25.8	25.6	27.5
65 to 74 years	7.0	8.7	8.9	7.9	9.9
75 to 84 years	3.0	6.3	6.5	5.6	7.3
85 years and older	1.0	2.6	2.7	2.4	2.7
Total	100.0	100.0	100.0	100.0	100.0

Table 2: Mortality and average excess of death in Sweden and by region, for 8 seasonal years (week 27-2001 to week 26-2009),

	Regions of Sweden			Total Sweden *
	South	East	North	
Population	3956981	3440869	1705586	9103436
Total number of deaths / year	40253	30978	20026	91257
Expected number of deaths / year	39367	30485	19703	89333
Mortality rate / 1000 / year	10.2	9	11.7	10
Age Standardised mortality rate / 1000 population / year	**5.5**	**5.5**	**6**	**5.6**
Total excess above baseline mortality / year	886	493	324	1924
Average excess rate /100 000 population / year	22.4	14.3	19	21.1
Excess / 100 deaths / year	2.3	1.6	1.6	2.2
Average age standardised excess rate /100 000 population / year	**10.9**	**8.6**	**7.6**	**10.8**
Z-score of excess	**9.8**	**7.1**	**3.7**	**12.4**

*** expected number of death and related indicator are based on the model applied for all Sweden, and is not the total of the results by regions**

Table 3: Excess mortality, Total and attributed to seasonal influenza A, pandemic influenza A and extreme temperature in Sweden for each seasonal years (from summer to spring) from 2001 week 27 to 2010 week 8 *

	Seasons, from week 27 to week 26 of each years								
Year of Period Start	2001-2002	2002-2003	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009	2009-2010
Duration of the Study Period	52	52	52	53	52	52	52	52	35
TOTAL									
Total number of deaths	92320	92730	89677	93856	88585	91416	90384	91085	59003
Expected number of death	91021	90110	89223	89967	87952	88894	89523	87705	57832
Total excess of death above a cyclical seasonality	[395-203]	[1880-3360]	[-344-1253]	[3196-4583]	[-146 - 1413]	[3221-1822]	[37-1686]	[2617-4144]	[439-1902]
Z-score	2.3	6.1	1.0	9.0	1.5	6.1	2.0	8.1	3.4
INFLUENZA A Seasonal									
Predominant strain	H3 90%	H3 90%	H3 90%	H1 30% H3 70%	H1 40%, H3 60 %	H3 90%	H1 90 %	H3	H3
Circulation	High	Low	High	High	Low	High	Low	High	Low
Excess of deaths	1395	325	1504	2494	611	1288	575	1866	195
95 % CI	[1219 - 1571]	[284 - 366]	[1314 - 1694]	[2082 - 2906]	[510 - 712]	[1125 - 1450]	[115 - 1036]	[1631 - 2102]	[164 - 227]
Z-score	3.33	0.8	3.53	5.75	1.5	3.08	1.35	4.43	0.61
Specific mortality rate	15.3	3.6	16.5	27.4	6.7	14.1	6.3	20.5	2.1
INFLUENZA A H1N1 (2009)									
Excess of deaths									199
95 % CI	-	-	-	-	-	-	-	-	[-105 - 503]
Z-score									0.58
Specific mortality rate									2.2
COLD									
Excess of deaths	224	743	148	174	345	215	0	171	1198
95 % CI	[179-269]	[593-892]	[118-178]	[139-209]	[276-415]	[172-259]	[00]	[136-205]	[957-1439]
Z-score	0.53	1.7	0.35	0.4	0.83	0.52	0	0.41	2.87
Specific mortality rate	2.5	8.2	1.6	1.9	3.8	2.4	0.0	1.9	13.2
HEAT									
Excess of deaths	170	327	209	97	170	362	87	166	106
95 % CI	[104-236]	[200-454]	[127-290]	[59-135]	[104-236]	[221-503]	[53-121]	[101-231]	[65-148]
Z-score	0.22	0.82	0.53	0.25	0.43	0.92	0.22	0.43	0.34
Specific mortality rate	1.9	3.6	2.3	1.1	1.9	4.0	1.0	1.8	1.2

* Only the first 8 weeks could be study in 2010 corresponding to a season of 35 weeks. Z-scores account for that shorter period of time.
** per 100,000 population

Figure 1: Weekly number of deaths and excess of deaths attributed to Influenza A and extreme temperatures, Sweden 2001 week 27 to 2010 week 8

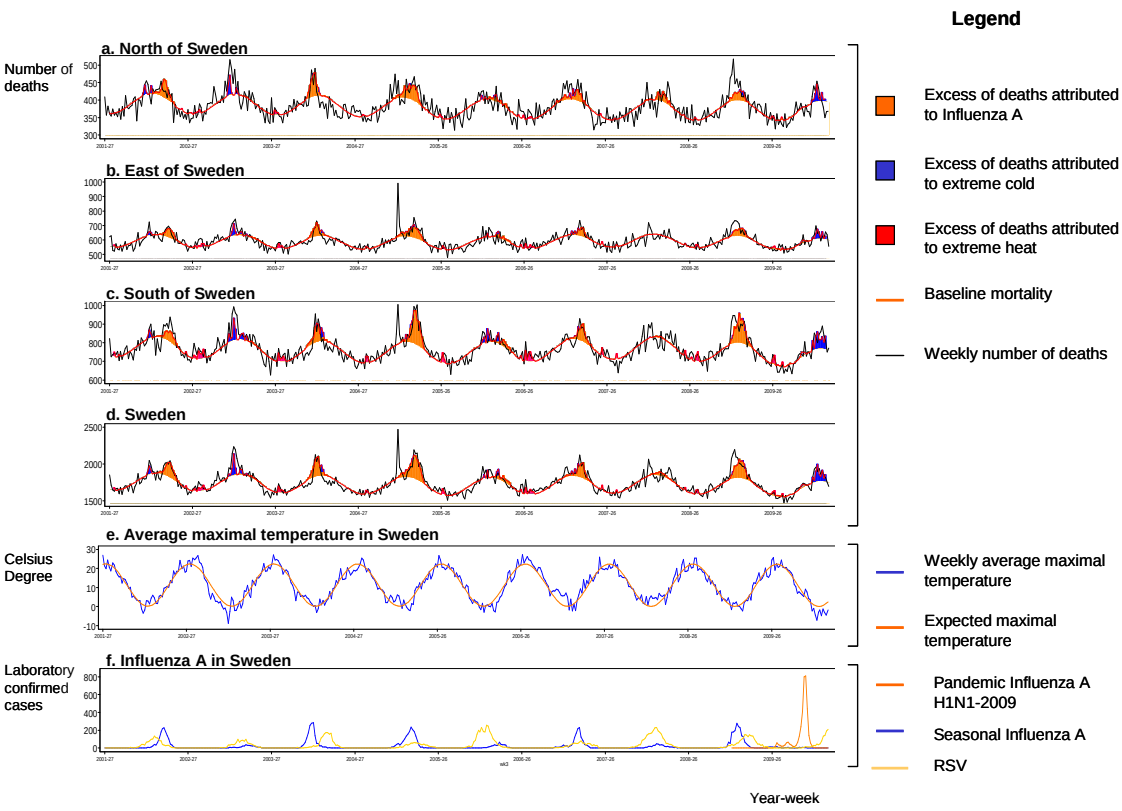


Figure 2: Excess rate (specific mortality) attributed to influenza A, Extreme cold and extreme heat, associated Z-score and 95 % confidence intervals, , by region of Sweden, between week 27-2001 and week 8-2010.

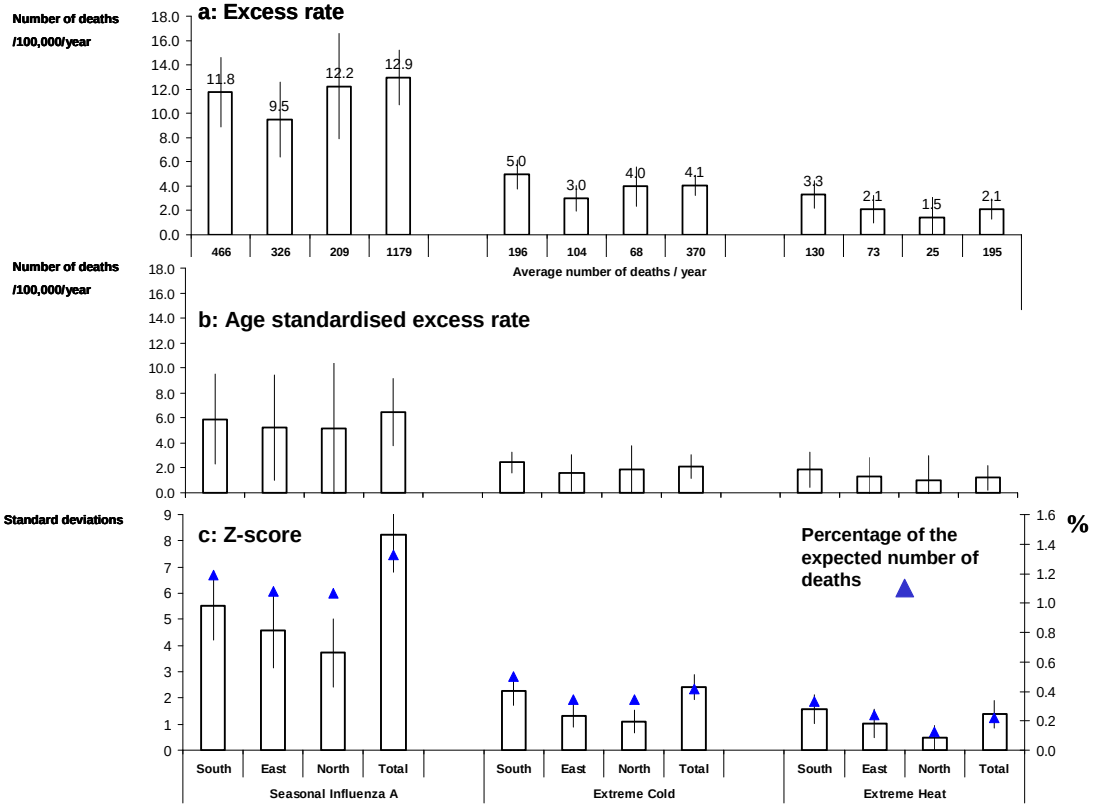


Figure 3: Excess rate (specific mortality) attributed to influenza A, Extreme cold and extreme heat, associated Z-score and 95 % confidence intervals, by age group, Sweden, between week 27-2001 and week 8-2010.

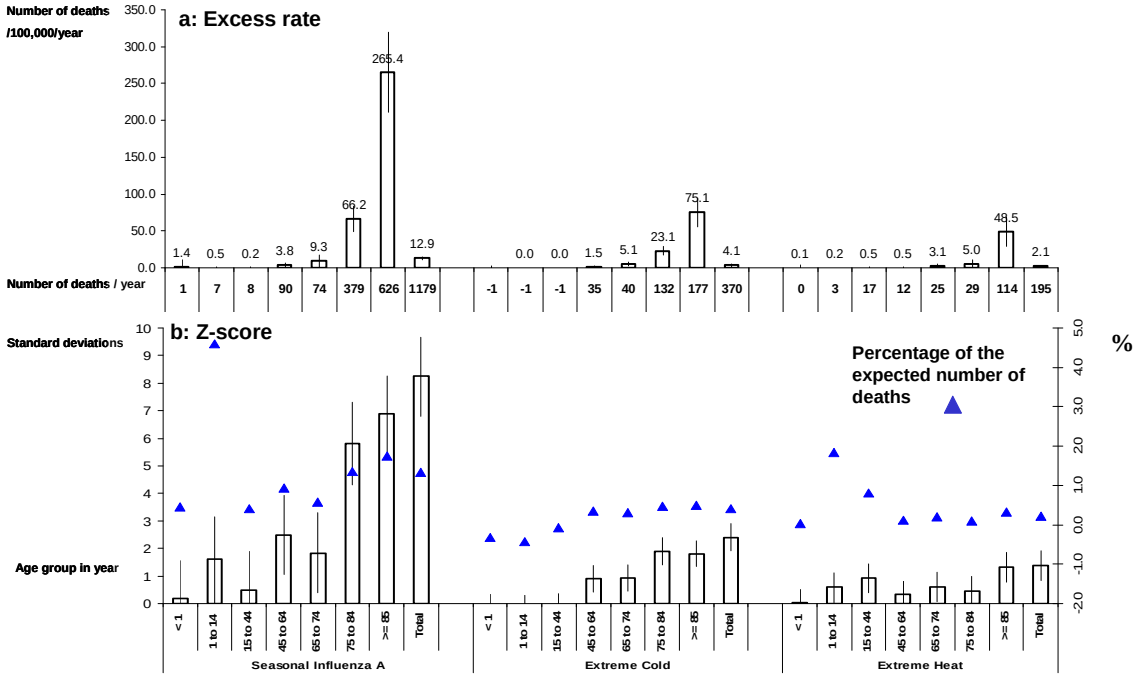
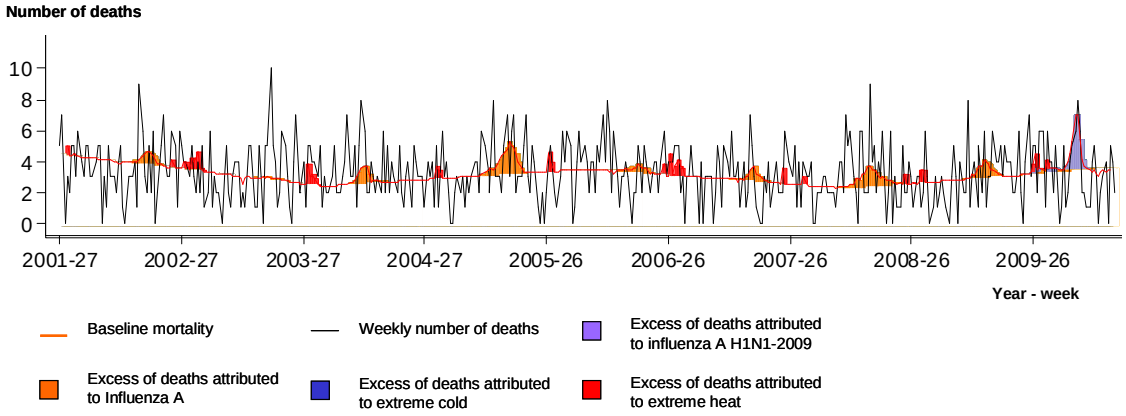


Figure 4: Weekly number of deaths and excess of deaths attributed to Influenza A and extreme temperatures in the 1 to 14 years children, Sweden 2001 week 27 to 2010 week 8*



* To facilitate the reading of the graph, the peak of mortality related to the 2004 tsunami in that age group was removed from the series.

Table 4: Association between weekly mortality and extreme temperatures (cold and heat) in the 3 regions of Sweden, 2001 to 2010.

	Extreme cold			Extreme heat		
	Increase of mortality for one Celcius degree decrease below the expected minimal temperature			Increase of mortality for one Celcius degree increase above the expected maximal temperature		
Region of Sweden	Expected minimal temperature in Winter (℃)	n	%	Expected maximal temperature in Summer (℃)	n	%
North	-2.7	5.2	1.5	21.2	2.5	0.6
East	-0.4	8.7	1.6	23.1	6.7	1
South	1.75	17.8	2.5	22.5	12.3	1,5

2.1.2 Excess Mortality Related to Outbreaks of Influenza, Respiratory Syncytial Virus and Norovirus in Sweden 2003-2010

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Introduction

Already in the 1830ies the first observations of the relation between influenza outbreaks and high winter mortality were made, and in the 1850ies the concept of excess mortality was established. Since influenza infections leading to death are only infrequently noted as cause of death at the death certificate, various methods for estimation of excess mortality have been suggested. Today it is usually calculated by the use of models with baseline seasonal death, mortality above a certain standard deviation is then designed as "excess" [1]. Markers for influenza activity that may cause excess deaths have often been reported weekly numbers of laboratory verified influenza diagnoses [2,3] or deaths with influenza given as the cause of death at the death certificate [4]. An influenza severity index has also been suggested [5] to adjust for the varied pathogenicity of different types and subtypes of influenza.

However, many viral epidemics apart from influenza occur in the winter period, and these outbreaks are often simultaneous with high influenza activity. Above all respiratory syncytial viruses (RSV) [3] and noroviruses (NoV) [6] have been suggested to contribute to excess mortality. If not included in the analysis, these simultaneous events may give falsely high numbers for influenza related mortality [7]. Also, excessively cold periods, low access to health care during Christmas holidays and other season related factors contributing to the excess winter mortality may confuse the picture [8-10]. Multivariate analyses including more viruses than influenza and RSV have to our knowledge not been published.

In Sweden, since 1994, we have based out estimates of excess influenza mortality on a smoothed baseline calculated from the number of deaths during years when no laboratory verified influenza diagnoses were reported to the national surveillance system during a specific week. The influenza related excess mortality estimated by that method has been in the range of 10 (The season 2005-2006) to 40 (1993-1994) with a mean of around 25 excess deaths per 100 000 persons yearly, diagram available from: [http://www.smittskyddsinstitutet.se/publikationer/arsrapporter-och-verksamhetsberattelser/smis-arsrapporter-om-influensasasongen/], similar to what has been presented in other studies [3,4]. Though the correction for influenza presence has improved the specificity of the calculation, it does not take into account simultaneous events that affect mortality, as discussed above. Further, during epidemics different age groups may be affected at different times with spread of the epidemic. Infections in the old and vulnerable that often die related to influenza often occur after the peak among younger individuals.

To get estimates of the separate contributions of more than one factor, in this study we have developed a Generalized Additive quasi-Poisson regression model (GAM) [11] allowing for overdispersion for analysis of excess mortality in Sweden for persons aged 65 years and older with respect to influenza, RSV and NoV for the time period 2003-2010.

Methods

Laboratory diagnoses of influenza, RSV and NoV

All laboratories performing diagnostics for influenza, RSV and NoV infections in Sweden report all diagnoses and the sex and age of the patients weekly to the Swedish Institute for Infectious Disease Control (SMI). Weekly data for influenza are available since 1993, for RSV since 2000 and for NoV since 2003.

The weekly number of reports from autumn 2003 to spring 2010 for persons 65 years and older were used for the analysis of excess mortality. Denominator data and exact methodology for diagnoses used in the individual reporting laboratories are not known. However, the number of laboratories reporting has been constant and methods used for diagnosis are estimated to have been relatively constant as well.

Mortality data

All deaths are reported to Sweden statistics, and SMI gets an update of the number every 2nd week, including age and sex of the diseased. The completeness of the reporting of deaths to Sweden statistics increases with time, and the reporting is relatively complete after one month. Since all the data used concerned deaths more than half a year before, it has been regarded to be complete. Weekly numbers of deaths in persons aged 65 years and older were used for analysis.

Statistical analysis

The number of weekly reported deaths for individuals aged 65 years and older was used as a response variable in a Generalized Additive Model (GAM). Since deaths are assumed to occur independently of each other, we assumed that the responses follow the quasi-Poisson distribution with a linear link function of explanatory variables denoting the mean value. The quasi-Poisson distribution also incorporates a scale parameter accounting for possible overdispersion in data. Explanatory variables were time, week number (ISO 8601), average temperature and the number of reported cases of influenza, RSV and NoV in the age group 65 years and older. For the three first variables, smooth spline functions were defined and estimated using the standard GAM methodology [11] to account for long time trends, seasonal variation and climate impact. Since no demographic data were used in the model, we have to account for the fact that natural mortality increases over time because of a growing and ageing population. Seasonal variation is sometimes modeled using harmonic functions [1] and sometimes categorical variables [4]. The GAM approach with regression splines is in some sense an intermediate method reducing the number of parameters in the model while still being able to fairly well capture the underlying complex variation. The temperature was calculated as a population weighted average of observed temperatures at 45 geographically spread-out weather stations in Sweden.

The three remaining variables denoting the weekly number of reported cases of influenza, RSV and NoV in the age group 65 years and older were treated as interval variables. Consequently, since we use a linear link function the excess mortality with respect to each of these variables is proportional to the number of reported cases. To account for varying pathogenicity of influenza, we introduced different variables for each season making it possible to estimate seasonal influenza severity indices [5]. A similar approach was considered for RSV and NoV, but since no clear distinction between seasons could be established we used only one variable for each disease.

Validity of the model was examined through fitted values, residuals and residual deviance. When plotting fitted values against observed data, it was observed that the model seem to capture most peaks except a few single weeks in 2008 and 2009 in observed mortality (Figure 1). There is also no systematic variation in residuals when plotted against each of the explanatory variables and no obvious outliers. Moreover, normality in the residuals cannot be rejected. Finally, the residual deviance turned out to be 566.8, which is indeed larger than the degree of freedom 320 but indicates a reasonable fit.

Results

Data description
The weekly numbers of reported diagnoses of RSV, influenza and norovirus infections in persons aged 65 years and older in relation to total number of diagnoses is shown in Table 1. The dominant influenza type for all seasons considered was A/H3 except in 2007/08 when both A/H1 and B circulated and in 2009/10 when pandemic influenza H1N1 dominated in the autumn. Since very few cases of the new influenza over 65 years old were reported, we chose to exclude that strain from the analysis. In Sweden the intensity of RSV-outbreaks follows a biannual pattern, where seasons 2005/06, 2007/08 and 2009/10 reported around 2700 cases in total. The intermediate seasons were considerably milder with 2008/09 as amoderately severe exception. Generally the number of NoV cases shows less distinct peaks compared to those of influenza but has gradually increased over time, with the most severe season 2008/09 with more than 8000 reported cases.

The baseline model
The analysis of variance of the model is presented in Table 2. All non-disease explanatory variables (time, week and temperature) turned out to be strongly significant. The model that incorporates the two first factors is defined as the baseline model, i.e. the estimated mortality in the population given no reported cases of influenza, RSV or NoV and without temperature effect, illustrated in Figure 1. In order to distinguish the effects of the diseases exclusively, we also define a baseline with temperature effect included. The total excess mortality per week attributable to influenza, RSV and NoV is then defined as the difference between the full model, i.e. the model with all explanatory variables included, and the baseline model with temperature effect. It is interesting to note that temperature had minimal impact on excess mortality in the range 10-15 °C, which is largely in concordance with the results presented in [12].

Effect on mortality of influenza, RSV and NoV
Table 2 also shows that each of the three infections contribute significantly to the mortality in the age group 65 years and older. Influenza was the most influential, but both RSV and NoV turned out to be significant at the 5 % level. The estimated number of excess deaths attributable to each infection per week can be obtained as the number of reported cases multiplied by the corresponding parameter estimate. This is illustrated in Figure 2. Again, it is quite clear that influenza produces the largest number of excess deaths. In four seasons, when the number of influenza cases peaked, it exceeded 200, which corresponds to approximately 12 % of all reported deaths in this age group.

We also calculated the aggregated numbers of excess deaths per infection separately for the seven seasons studied with 95 % confidence intervals, which is shown in Table 3. The parameter estimate for influenza in season 2005/06 turned out to be negative, which is clearly unrealistic. Since it was not significant we chose to remove it altogether to avoid overestimation of the effect of the other diseases. Influenza was found to be the most severe infection with approximately 1000 excess deaths per season, but also that around 240 deaths can be attributed to RSV and 580 to NoV.

Discussion

The exact contribution from the described viruses and other factors causing excess mortality will probably never be fully understood. However, by introducing reliable surrogate markers and adequate statistical methods we may approach the truth. The difference from this study, in relation to most others, is that laboratory reporting only in persons older than 65 years were used to identify the peaks. We may have missed some excess mortality related to the three infections in persons in

the upper middle age, but previous studies [4] have indicated that it is relatively small in that age group.

In Sweden, there is also sentinel-reporting from general practitioners covering approximately 1% of the population. However, in these reports elderly are invariably under-represented. Severely ill persons seek the emergency wards without consulting GPs, and for treatment reasons as well as for logistic reasons (verified influenza, RSV or NoV cases can be cared for in the same room), specimens are drawn for laboratory verification of the diagnosis. Thus severe diseases are best pictured by the laboratory diagnoses. Further it is only 25 laboratories that diagnose influenza, and we know that their reporting to SMI is very reliable in contrast to that from sentinel doctors, where the propensity to report is quite varying. We therefore think that "laboratory reports in 65+" are rather well chosen variables. At least for influenza it seems that the results also correlate well with what has been reported from other countries.

Regression models of various designs have previously been used to estimate influenza- and RSV-attributable deaths [3,4,13-15], but no attempt has been made to incorporate NoV. These models are very flexible and have the ability to distinguish between several different effects and causes of excess mortality. Moreover, it is possible to quantify all causes separately in order to evaluate time trends, seasonality and, most importantly, the severity of various circulating viruses and other pathogens in the population.

The seasonal variation is sometimes modeled by harmonic functions like the sine and the cosine functions [14], which reduces the number of parameters in the model but imposes strong restrictions on the form of seasonal component. Mortality is very complex and can probably not be that easily captured. Another alternative, which was used in [4], is to model seasonality using categorical variables. In [4], month was used, but could very well be replaced by week, partly because mortality and disease data are usually presented on a weekly basis, but also to obtain a more detailed pattern of mortality. This is a more flexible way to approach the problem but introduces the burden of several additional parameters in the model, which usually improves the fit but decreases the significance of parameter estimates.

This method presents an intermediate alternative since the GAM methodology makes it possible to model relationships as smooth functions with a greater degree of flexibility than simple harmonic functions. In this study, the fitting process produced a cyclical seasonal spline function with 3.3 estimated degrees of freedom, in contrast to a harmonic function with 2 degrees of freedom and a categorical variable with 11 (month) or 52 (week) degrees of freedom. As a bonus, we could also capture the complex time trend and temperature effects with other smooth spline functions.

To summarize, the exact nature of excess mortality is embedded in a complex net of causal effects which we have little hope of ever disentangle. However, the improvements of existing surveillance systems and developments of new ones gradually give us access to data of better and better quality. This also poses a challenge to develop models that are able to incorporate new available data in order to better understand the underlying mechanisms. We feel that the model presented in this study is one step in this direction and that it may be adapted in other countries than Sweden.

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Table 1. Number of reported cases of influenza, respiratory syncytial virus (RSV) and norovirus (NoV) in total and for the age group 65 years and older

Season	Influenza			RSV			NoV		
	Total	**65+**	**Prop**	**Total**	**65+**	**Prop**	**Total**	**65+**	**Prop**
2003/04	1590	471	30%	1554	9	1%	641	288	45%
2004/05	2019	1080	53%	826	8	1%	2500	1781	71%
2005/06	924	222	24%	2626	93	4%	1835	1284	70%
2006/07	1374	551	40%	968	24	2%	5749	4518	79%
2007/08	1246	750	60%	2751	66	2%	4684	3492	75%
2008/09	2046	712	35%	1835	51	3%	8295	6227	75%
2009/10	163	17	10%	2705	72	3%	6047	4303	71%

Table 2**.** Analysis of variance of the model

Factor	**SS**	**MS**	**D.f.**	**F**	**p-value**
Time	52861	13656	3.9	5.00	<0.001
Week	82760	25109	3.3	9.20	<0.001
Temperature	68459	10045	6.8	3.68	<0.001
Influenza	625874	89411	7	32.76	<0.001
RSV	19681	19681	1	7.21	0.008
NoV	17536	17536	1	6.43	0.012
Error	873268	2729	320		
Total	5953285		343		

Table 3. The estimated number of extra deaths attributable to influenza, respiratory syncytial virus (RSV) and norovirus (NoV) per season with 95 % confidence intervals

Season	**Influenza**		**RSV**		**NoV**	
2003/04	1300	(940,1650)	50	(10,80)	50	(10,100)
2004/05	2430	(1960,2890)	40	(10,70)	330	(80,590)
2005/06	0	NA	490	(130,840)	240	(50,420)
2006/07	1190	(770,1620)	130	(30,220)	840	(190,1490)
2007/08	270	(-270,820)	350	(90,600)	650	(150,1150)
2008/09	1640	(1130,2140)	270	(70,460)	1160	(260,2060)
2009/10	140	(-260,530)	380	(100,650)	800	(180,1420)
Average	1000	(840,1160)	240	(70,420)	580	(130,1030)

Figures

Figure 1. Weekly number of reported deaths in age group 65 years and older. Observed data (black) against fitted data (red), baseline with temperature (blue) and baseline without temperature (green).

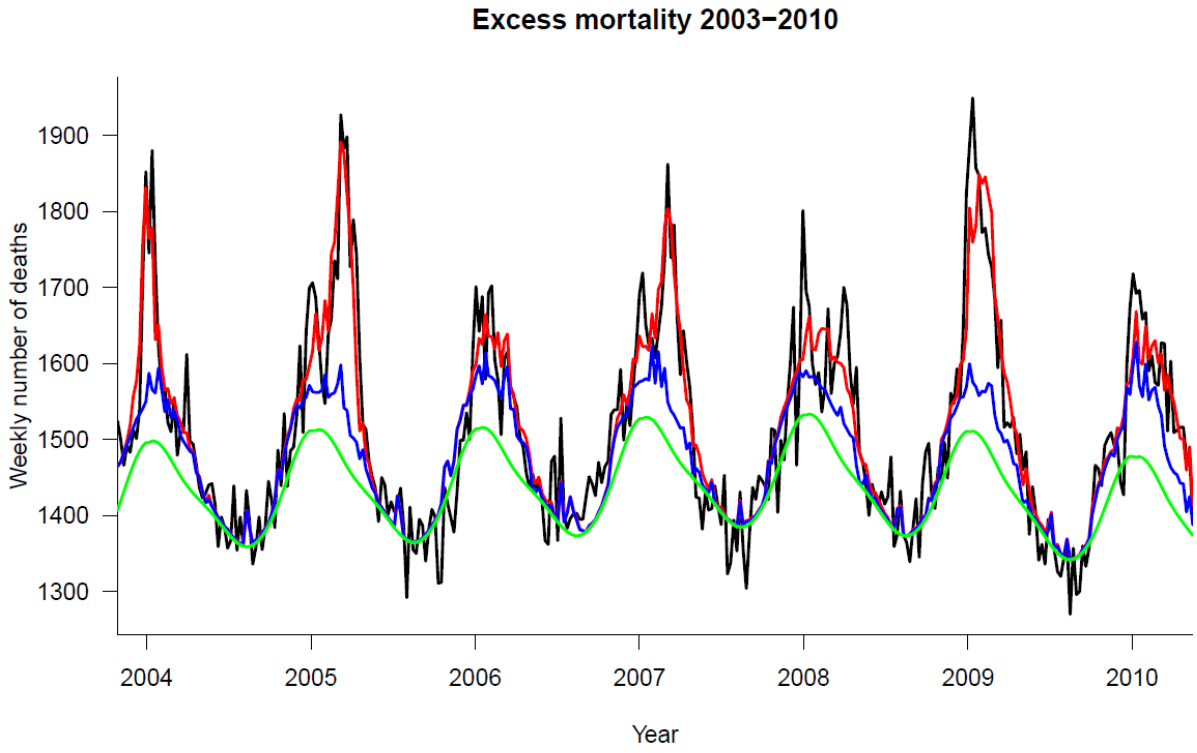
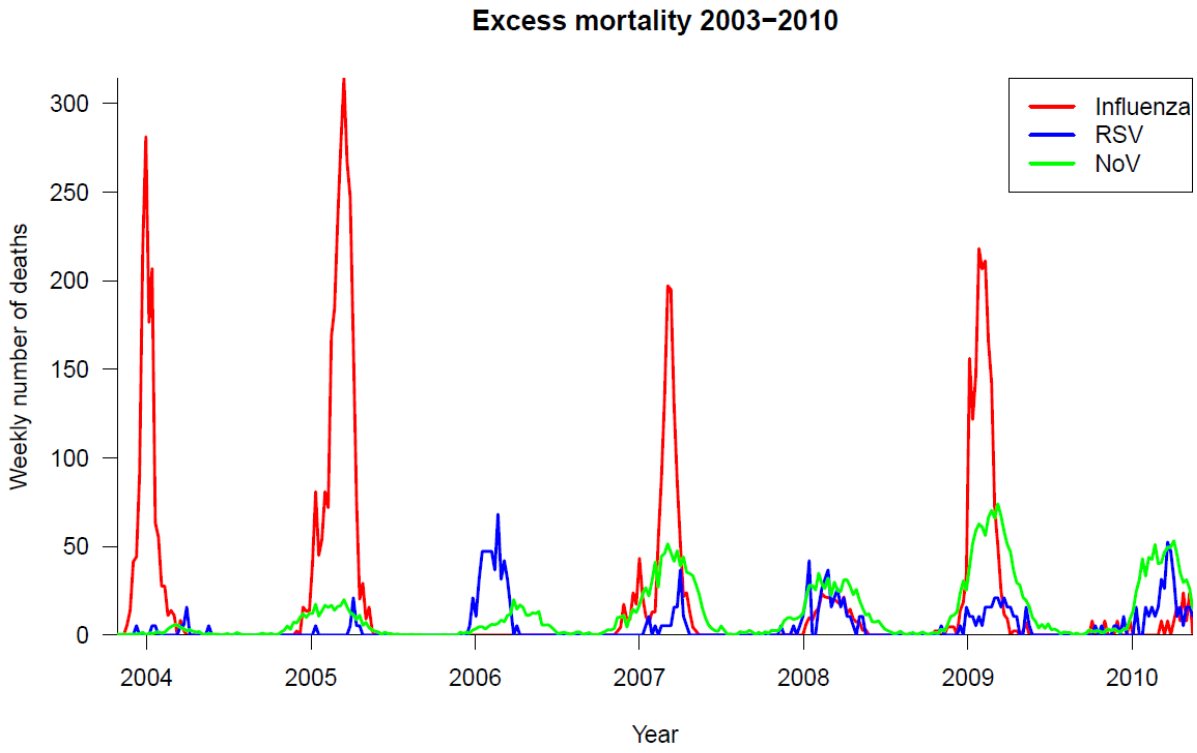


Figure 2. Estimated weekly number of deaths attributable to influenza (red), RSV (blue) and NoV (green).



2.2. Mortality in Denmark

Excess mortality related to seasonal influenza and extreme temperatures in Denmark, 1994-2010.

Jens Nielsen, Anne Mazick, Steffen Glismann, Kåre Mølbak

Abstract

To describe mortality related to influenza and periods with extreme temperatures in Denmark over the seasons 1994/95 to 2009/10, we applied a multivariable time-series model with all-cause mortality as outcome, activity of influenza-like illness (ILI) and excess temperatures as explanatory variables, controlling for trend, season, age, and gender. Two estimates of excess mortality related to influenza were obtained: (1) ILI-attributable mortality modelled directly on ILI-activity, and (2) influenza-associated mortality based on an influenza-index, constructed to mimic the influenza transmission. The median ILI-attributable mortality per 100,000 population was 35 (range 6 to 100) per season which corresponds to findings from comparable countries. Overall, 92% of these deaths occurred among persons ≥ 65 years of age. The median influenza-associated mortality per 100,000 population was 26 (range 0 to 73), slightly higher than estimates based on pneumonia and influenza cause-specific mortality as estimated from other countries. Further, there was a tendency of declining mortality over the years. The influenza A(H3N2) seasons of 1995/96 and 1998/99 stood out with a high mortality, whereas the A(H3N2) 2005/6 season and the 2009 A(H1N1) influenza pandemic had none or only modest impact on mortality. Variations in mortality were also related to extreme temperatures: cold winters periods and hot summers periods were associated with excess mortality.

We conclude that it is doable to model influenza-related mortality based on data on all-cause mortality and ILI; data that are easily obtainable in many countries and less subject to bias and subjective interpretation than cause-of-death data. Further work is needed to understand the variations in mortality observed across seasons and in particular the impact of vaccination.

Introduction

In temperate zones, all-cause mortality exhibits a marked seasonality with the highest number of deaths in the winter and a lower number in the summer period. The reasons for this pattern are complex and not completely understood. Many factors may contribute, including increased rates of acute respiratory tract infections and death from cardio-vascular diseases in the winter months, periods with extreme temperature, and possibly mental and physiological effects (e.g., D-vitamin) related to day-light as well as social and psychological factors related to Christmas and New Year holidays [Philips 2010]. However, it is well recognised that one of the main causes of winter excess mortality is influenza.

There is a long tradition of using statistical models based on mortality from respiratory illnesses (Pneumonia and Influenza: PI) or all-cause mortality for estimating the number of deaths related to influenza. Different authors have applied different estimation methodologies. The most commonly used methodology, often called Serflings method, estimate the expected mortality without influenza based on either predefined periods with no or ignorable influenza activity [Serfling 1963, Thompson 2009] or dynamically defined periods with no influenza activity categorised by influenza activity recorded under a certain level e.g. 95% confidence limit; influenza activity have been defined by influenza specific mortality [Viboud 2004, Simonsen 2005, Rizzo 2007, Cohen 2010], or Influenza Like Illness (ILI) reported from networks of sentinel practices [Nogueira 2009, Brinkhof 2006,

Denoeud 2007] or reported as surveillance counts for laboratory virus-positive specimens [Newall 2009, Cohen 2010]. Hence, periods with influenza-attributable mortality may vary from season to season and according to each season's influenza activity. Excess mortality attributable to influenza is then calculated as the observed minus the modelled expected mortality without influenza as estimated from periods without influenza activity. Others has extended the estimation of the no-influenza expected mortality to exclude impact of other respiratory and circulatory diseases, like Respiratory Syncytial Virus (RSV), by controlling for presence of these in the estimation of the expected no-influenza mortality [Brinkhof 2006, Newall 2010, Kwong 2008]. Instead of excluding periods with influenza activity from the estimation of the no-influenza expected mortality, these periods may be down-weighted [Farrington 1996]. Alternatively, influenza activity can be included directly as a parameter in a multivariable time-series model, then often using an identity-link, including influenza activity, trend and seasonal variation as independent variables [Tillett 1980, Thompson 2009, Newall 2009, Wong 2004]. Thus, in this latter approach excess mortality is determined directly from data on influenza and not as a residual difference.

Ambient temperature may also play a role in the seasonal variation of mortality [Tillett 1980, Diaz 2005, Yang 2008, Revich 2010, Joacim 2010], but this is often not included in assessment of influenza-related mortality.

The aim of the present study was to describe mortality associated to influenza and periods with extreme temperatures in Denmark over the seasons 1994/95 to 2009/10.

Materials and methods

To investigate the impact of influenza and extreme temperatures on mortality we specified and applied a multivariable time-series model with all-cause mortality as outcome, influenza activity and excess temperatures as explanatory variables, and controlled for trend, season, age and gender.

Data sources

Data for the analyses were obtained from the following sources:

Individual notifications of deaths were obtained from the Danish civil registry system by the Department of Epidemiology, SSI, in the form of daily electronic notifications of all deaths.

The sentinel influenza surveillance system based on primary health care consultations was established in 1994 as a voluntary reporting system of general practitioners providing weekly reports on the total number of consultations and age-specific numbers of Influenza-Like-Illness (ILI) consultations to the Department of Epidemiology, Statens Serum Institut (SSI). This system is usually discontinued in the summer period between week 20 and 40, but in 2009 data were collected throughout the year.

Data on daily temperatures registered at Danish weather stations was downloaded from the National Oceanic and Atmospheric Administration Online Climate Data Directory [NOAA]. Mean over daily temperatures from all weather stations was used as the overall Danish temperature for that day. Weekly temperatures were calculated as the mean over the week. Using these weekly temperatures, we estimated the expected weekly temperature in a General-Linear-Model with a sine seasonal variation (Figure 1), and the difference between observed and expected were used to express weeks with extreme positive or negative temperatures.

Size of the Danish population by age and gender on the 1st of January every year was downloaded from Statistics Denmark [StatBank] (Table 1). The weekly sizes of the age group and gender specific populations were achieved by linear interpolation.

Analyses

In our primary analysis, termed ILI-attributable mortality, we fitted a model with the weekly all cause number of death as outcome and ILI-activity and extreme temperatures as independent variables and adjusted for trend, seasonal variation, age and gender.

Influenza circulates simultaneously with other respiratory tract infections that may have been reported as ILI, especially in autumn and spring, i.e. in the beginning and end of the influenza season. To get an indication of the part of ILI associated with mortality associated with influenza we did a sub-analysis, where we reduced ILI in the beginning and end of the period with activity; based on the assumption that the major part of ILI will be influenza at the peak whereas influenza will not be a major contributor to ILI when ILI is low. This analysis was termed influenza-associated mortality.

Statistical analyses

To estimate the association between weekly mortality, and influenza activity and extreme temperatures for the seasons 1994/5 to 2009/10 (week 27, 1994 to week 26, 2010), we used a multivariable time-series model with calendar week (wk) as underlying time unit, stratified by age groups (a = 0, 1-4, 5-14, 15-44, 45-64, 65-74, 75-84, 85+ years) and gender (g):

$$E(MR_{a,g,wk}) = E(D_{a,g,wk}/N_{a,g,wk}) = E(D_{a,g,wk})/N_{a,g,wk}$$

where MR is the Mortality Rate, D number of all-cause deaths and N is the none-stochastic size of the population.

We used an additive Poisson regression model (link = id) with 1/population-size as exposure parameter and allowing for overdispersion. For each age group and gender, the model for E(D) could formally be described as (omitting regression constants and parameters to be estimated):

$$\begin{aligned} E(D) = {} & \text{spline}(wk) + \\ & \sin(2\pi(365.25/7)*wk) + \cos(2\pi(365.25/7)*wk) + \\ & \sin(4\pi(365.25/7)*wk) + \cos(4\pi(365.25/7)*wk) + \\ & \textstyle\sum_s\sum_{wk} IA + wc_{wk} + ww_{wk} + sc_{wk} + sw_{wk} + \\ & \textstyle\sum_s\sum_{wk-1} IA + wc_{wk-1} + ww_{wk-1} + sc_{wk-1} + sw_{wk-1} + \sum epi \end{aligned}$$

where the terms spline(wk) and the sine and cosine terms express the baseline with trend and seasonality. Trend was included as a cubic spline, and both a yearly and half-yearly seasonal cycles were included as sines and cosines. Impact of influenza activity (IA) $\sum_s\sum_{wk} IA$ was in the primary analysis expressed as proportion of weekly ILI-consultations (percentage of consultations with ILI) on number of deaths in each season s (season: week 27 to week 26 the following year). Impact of extreme temperatures were separated in weeks with extreme summer or winter temperatures (warm: weekly minimum temperature > expected weekly temperature; cold: weekly maximum temperature < expected weekly temperature) and include as the four variables: wc = winter cold, ww = winter warm, sc = summer cold and sw = summer warm) (Figure 1). Further, deaths may be delayed relative to when IA was registered at a consultation or relative to when the temperature was extreme. Therefore, IA and extreme temperature event from the presiding week were also included. Finally, to compensate unexplained peaks (outliers), residuals greater than 1.5 standard deviations, lasting 3 week or more and not explained by IA or extreme temperatures were included as artificial epidemic-parameters to compensate these ($\sum epi$).

In order to obtain a more conservative estimation of influenza-associated mortality (rather than ILI), we applied an influenza-index to express influenza activity (IA), created by reducing the ILI consultation percentage for each season. This was done by multiplying

the ILI consultation percentage in a specific season with a normal distribution, with mean and standard derivation as for the ILI percentage over the same season. This reduces the ILI percentage in the beginning and end of the season, and maintains the ILI percentage at the height of the season (Figure 2).

In the final model only trend and seasonal yearly or half-yearly cycles were included if they contributed on a 5% level ($p<0.05$). Results are reported for the age groups 0-4, 5-14, 15-64 and 65+ years of age and for both sexes together. Hence, the results were adjusted for heterogeneities in pattern and variations between ages and genders. All analyses were done using Stata 11 MP.

Results

The model fitted well in all age and gender strata (examined on deviances [McCullagh 1989]), and there were no indications of either heteroskedasticity or residual autocorrelation. The results of the model are shown in figure 3 for age groups and gender.

We found mortality to be associated with both ILI-activity and extreme temperatures (Figure 4).

The model included a baseline with both a yearly seasonal cycle and a half-yearly cycle, and the half-yearly cycle contributed on a 5% level in most strata. However, this was not due to a summer peaks; the half-year cycle created a seasonal pattern where the total seasonal cycle reaches its maximum earlier than for a symmetric yearly cycle, and as a consequence the decline became prolonged (baseline in figure 4), corresponding more to the appearance of slightly asymmetric “epidemic curves” including a long right tail.

ILI-attributable mortality

Over the seasons 1994/5 to 2009/10 the total median number of excess deaths per season attributable to ILI was 1882 (range: 306-5251) and the median mortality rate (MR) per 100,000 population was 35.4 (range: 5.6-100.0), table 2. Most of the ILI associated deaths was among elderly ≥ 65 years (median 92.3%) and adults 15-64 years (median 15.2%). There were nearly no ILI associated excess deaths among children (median 4 deaths for 0-4 years and -1 for 5-14 years of age), table 2.

Among adults, 15-64 years, there was an estimated annual number of ILI-associated deaths of 286 (range: -185 to 531) and the MR per 100,000 was 8.0 (range: -5.3 to 15.0). Among persons aged 65 the median number of deaths was 1738 (range: 365 to 4723) corresponding to a MR per 100,000 of 206.7 (range: 44.4 to 593.6). All estimates were adjusted for variations over age and between genders.

Influenza-associated mortality

All reported ILI-cases are not influenza. Hence, we reduced the ILI consultation percentage according to a pattern that reflected influenza-transmission (Figure 3). Compared to the total ILI-attributable number of deaths, this reduced the median total number of excess deaths with around 25% to 1420 (range: -8 to 3810) per season per 100,000, and MR to 26.4 (range: -0.1 to 72.6) (Table 3). Overall, we estimated that 82.0% of the influenza-associated deaths were among elderly aged 65 years.

Temperature associated mortality

A yearly median of 39 deaths (range: -162 to 273) could be attributed to extreme ambient temperature, this corresponded to a MR per 100,000 of 0.7 (range: -3.0 to 5.2). These estimates were adjusted for variations over age and between genders (Table 4). The impact of extreme temperatures on mortality varied between benign (life saving) and malign (increased mortality) effects over the seasons, except among adults (15-64 years

of age) where only malign effects of extreme temperatures were estimated. Further, a summer and winter differentiation in the impact of warm and cold temperatures was observed, with a benign effect of extreme cold during summer and the opposite in winter. For extreme warm temperatures it was the other way around (Table 5).

Discussion

Over the seasons 1994/5 to 2009/10 we found a median all-cause mortality rate of 35.4 (range: 5.6-100.0) per season per 100,000 attributable to ILI for all ages and all inhabitants in Denmark, adjusted for trend, seasonality, extreme temperatures and heterogeneities between age groups and genders. This was within the range of estimates from Germany, USA, Italy and Canada based on all-cause mortality (Table 6) (range: 10 to 90 deaths per season per 100,000). However, it is important to underline that these estimates were obtained using different models and different periods.

The most vulnerable age group for influenza death is the elderly with 80-90% of influenza related deaths among persons aged 65 [Tillett 1980, Rizzo 2007, MMWR 2010, Shindo 2000, Wong 2004]. We estimated the median Danish ILI-attributable mortality rate for persons aged 65 to 206.7 (range: 44.4 to 593.6), corresponding to 92% of all ILI deaths. Hence, our estimate of the all-cause mortality attributable to circulating influenza for persons aged 65 was slightly higher compared to estimates from other countries (table 6); probably, because of differences in age distributions and because they were estimates from earlier time periods.

Surveillance of ILI, will include other respiratory infections that may be perceived as influenza-like illness. Hence, excess mortality attributable to circulating influenza will over-estimate mortality associated to influenza. Therefore, PI as cause of death has been used to estimate influenza-associated mortality [MMWR 2010, Rizzo 2007, Viboud 2004, Wong 2004, Denoeud 2007]. Using PI-specific mortality has been found to reduce mortality attributable to circulating influenza with 38% among Swiss elderly (60+) [Brinkhof 2006], and 40% for all ages in Canada [Schanzer 2007] compared to estimates based on all-cause mortality. However, for various reasons, estimates based on PI as cause of death may tend to under-estimate influenza-associated mortality. Death due to influenza, or where influenza was an important component in the chain of events that lead to the death, may not be coded as respiratory, but rather as cardiac or related to complications of severe illness.

We estimated mortality attributable to ILI directly as a parameter in our model. To obtain estimates of influenza-associated mortality, we could have used data from laboratory based surveillance instead of ILI. However, the virological surveillance of influenza in Denmark is not sufficiently systematic and detailed to be used directly as a parameter to model influenza-associated mortality. Although samples are collected by the sentinel practitioners, they usually collect only three times in a season, which means that the samples do not reflect the amount of circulating influenza, i.e. are not suitable for modelling. Likewise, data on clinical samples from hospitals are, except for the 2009/10 pandemic, few in numbers for many seasons. We therefore used a proxy to downgrade ILI to influenza as described above, and estimated an all-cause influenza-associated mortality of 26.4 (range: -0.1 to 72.6) per season per 100,000, corresponding to a 25% lower mortality compared to ILI-estimates, and slightly higher than PI-associated mortality reported from other countries (table 6). Therefore, with mortality attributable to ILI being an over-estimate and PI-associated mortality probably an under-estimate our estimate, using the influenza-index, may well be a realistic estimate of influenza-associated mortality.

Mortality related to influenza has been found to be higher in season where the dominating influenza is H3N2, compared to H1N1 seasons [Simonsen 2005, Zucs 2005, Rizzo 2007, Cohen 2010, MMWR 2010]. We found particular high excess mortality in the two influenza A(H3N2) seasons of 1995/96 and 1998/99, whereas the influenza A(H3N2) season of 2005/6 and the 2009 influenza A(H1N1) pandemic had none or only modest impact on mortality. In addition, there has been a declining trend in influenza related mortality since the 1990's (Figure 5), remaining even if excluding the low-mortality 2005/6 H3N2 season and the 2009/10 H1N1 pandemic; though, not that strong. The reasons for this trend are not obvious, but increased use of vaccines for the elderly, genetic drift of the virus as well as herd immunity in the population may contribute.

Over the seasons 1994/5 to 2009/10 we found an all-cause median mortality rate of 0.7 (range: -3.0 to 5.2) per season per 100,000 attributable to periods with extreme temperatures for all ages and all inhabitants in Denmark, adjusted for trend, seasonality, influenza activity and heterogeneities between age groups and genders. However, this consists of both periods with extreme cold and heat, and covers both summer and winter. Perhaps not surprisingly, there seems to be a pattern where periods with cold weather in the summer is life saving, while heat may cost lives. In the winter season warm periods saves lives, while cold cost lives.

We have proposed and evaluated a methodology and statistical model usable to estimate excess mortality associated to two potential explanatory factors, ILI and extreme temperatures based on all-cause mortality. The model fitted data well and all-cause mortality has previously been found to be the most complete and accurate in assessing the total impact of influenza on mortality [Simonsen 1997]. More explanatory factors may be included in the model like for example RSV [Newall 2009], other cause of acute respiratory illnesses and invasive pneumococcal disease, to get more detailed estimates of variations in excess mortality. A limitation of the model is potential interactions between the explanatory factors, which cannot be easily implemented in the model; especially with more than two explanatory factors. To estimate mortality associated to influenza we used a robust methodology (the influenza-index) to segregate the influenza part of ILI. Others have used PI cause-specific mortality. Our methodology gives influenza-associated mortality in between the over-estimation using all cause mortality and the under-estimation using PI cause specific mortality. Further, it has the advantage of depending only on easily obtainable data namely weekly number of all-cause deaths, temperature, and ILI.

To sum up, we have shown that it is doable to model seasonally fluctuations in mortality related to ILI or influenza and to extreme ambient temperatures based on all-cause mortality. This is promising, as all-cause data is easier to obtain than cause-specific data, and not subject to coding bias as it is recognised that coding practices will be affected by awareness and media reports. However, it is of interest to apply our methodology to other datasets in order to validate it further. We also advocate that laboratory based influenza surveillance should be reinforced in order to better estimate the proportion of severe respiratory illness that are caused by influenza. This may serve as a more appropriate independent variable in future multivariable models. Finally, it is worth noting that influenza mortality has tended to decline, and that studies of the effect of vaccination policies on this trend are needed.

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Figure 1. Weekly Danish temperatures 1994/5 to 2009/10.

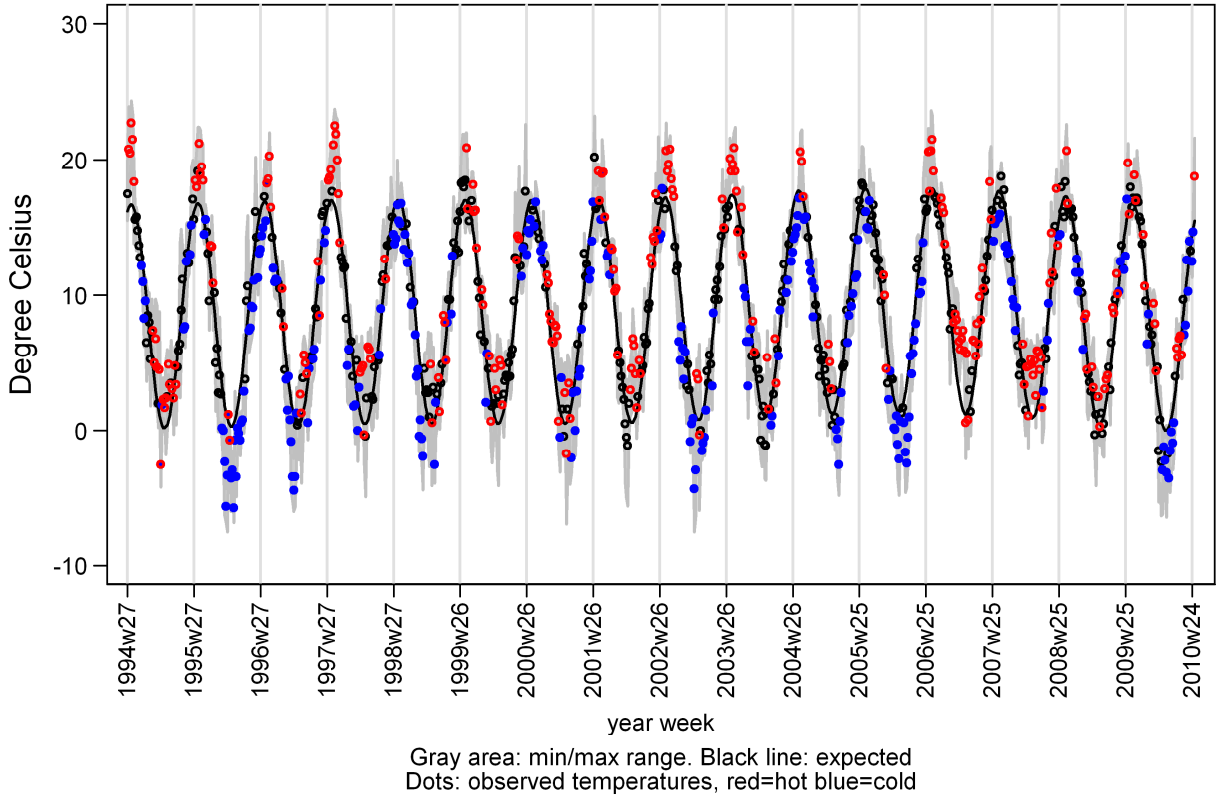


Figure 2. Influenza like illness consultation percentage and the influenza-index

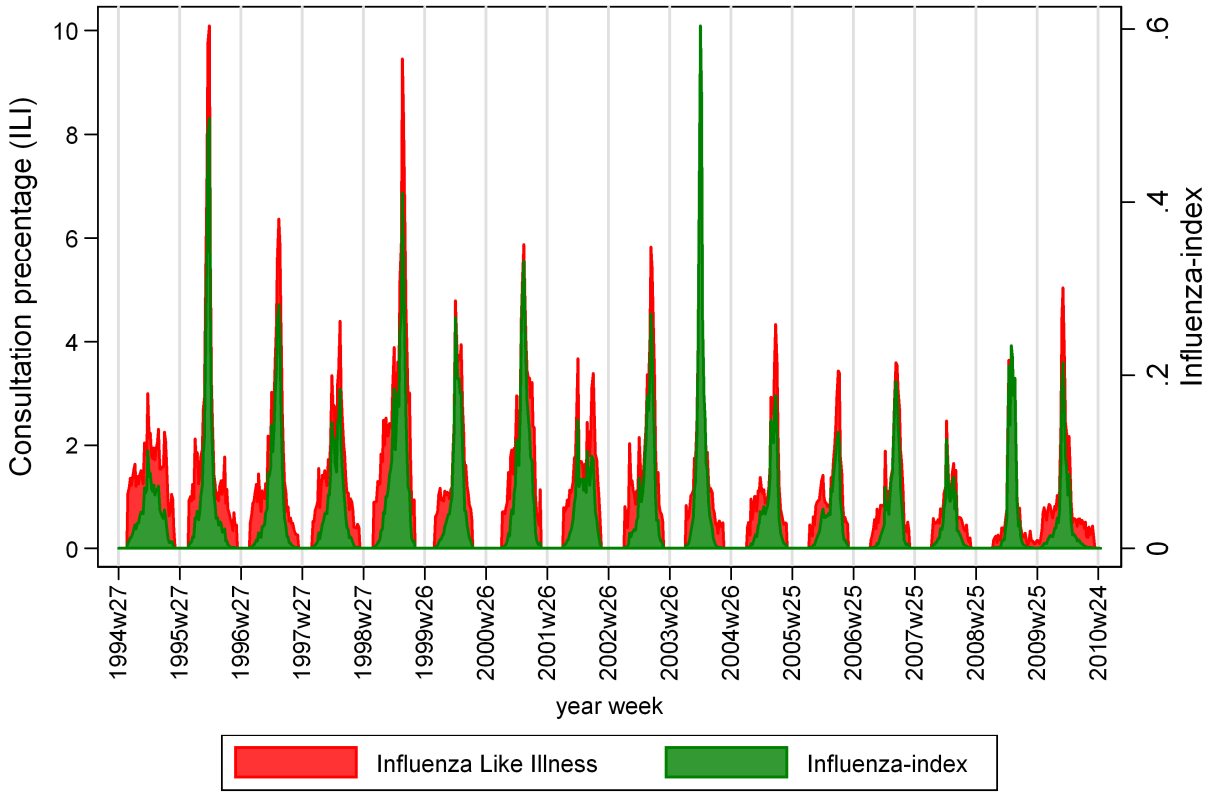
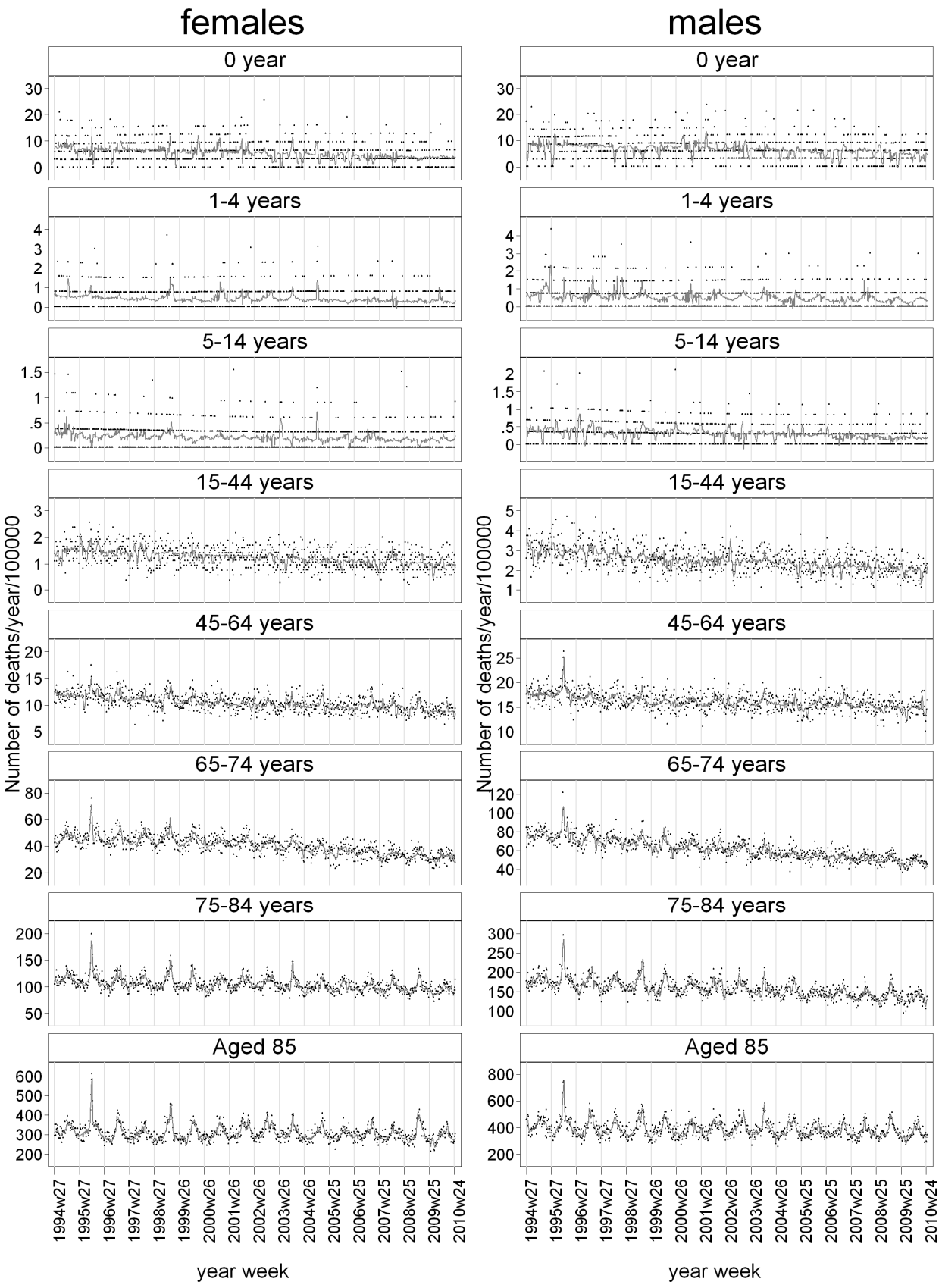
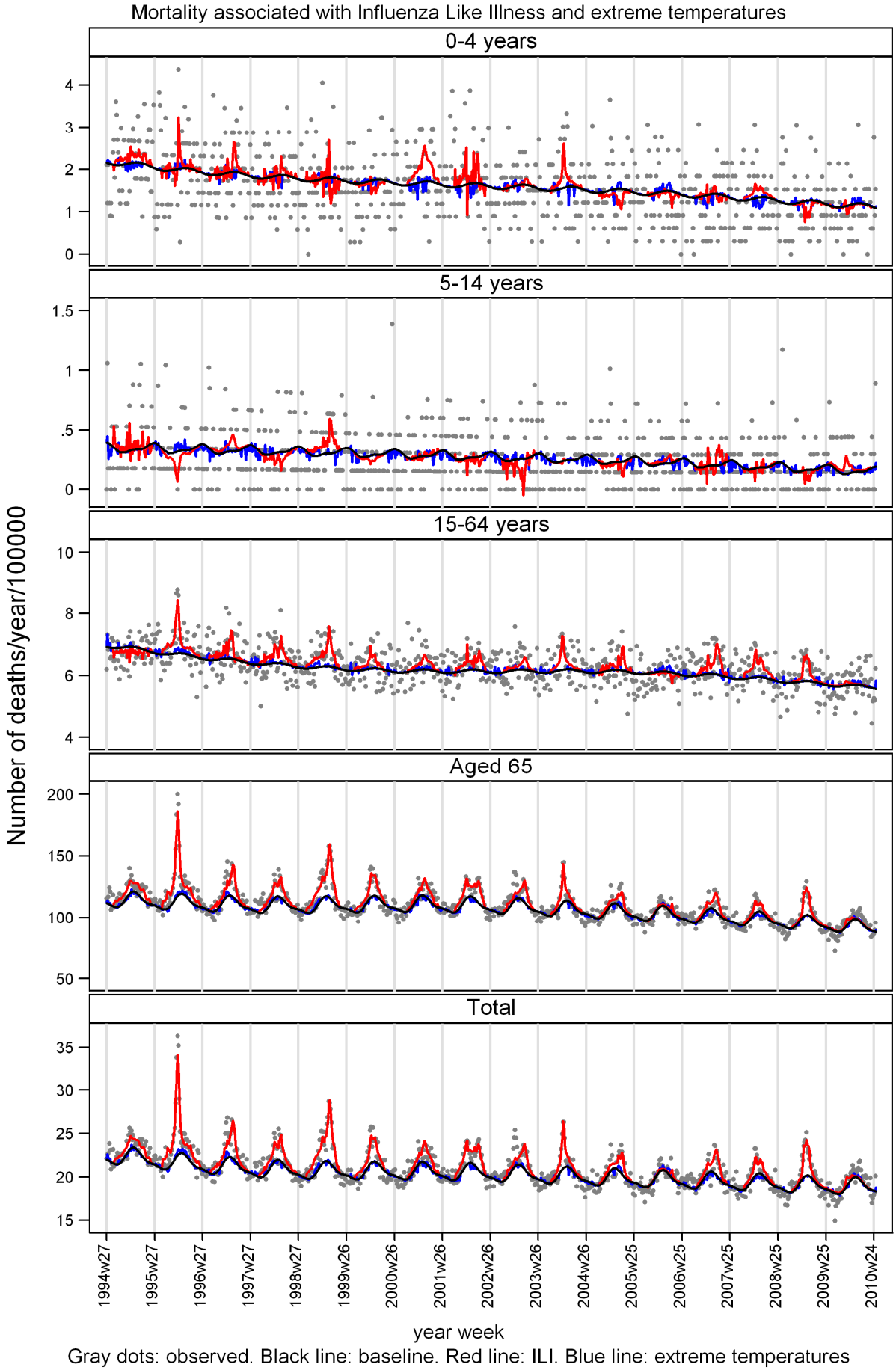


Figure 3. Final model



Black dots: observed. Gray line: final model

Figure 4. Mortality related to Influenza Like Illness and extreme temperatures



Gray dots: observed. Black line: baseline. Red line: ILI. Blue line: extreme temperatures

Figure 5. Influenza-attributable mortality, according to dominant type of influenza

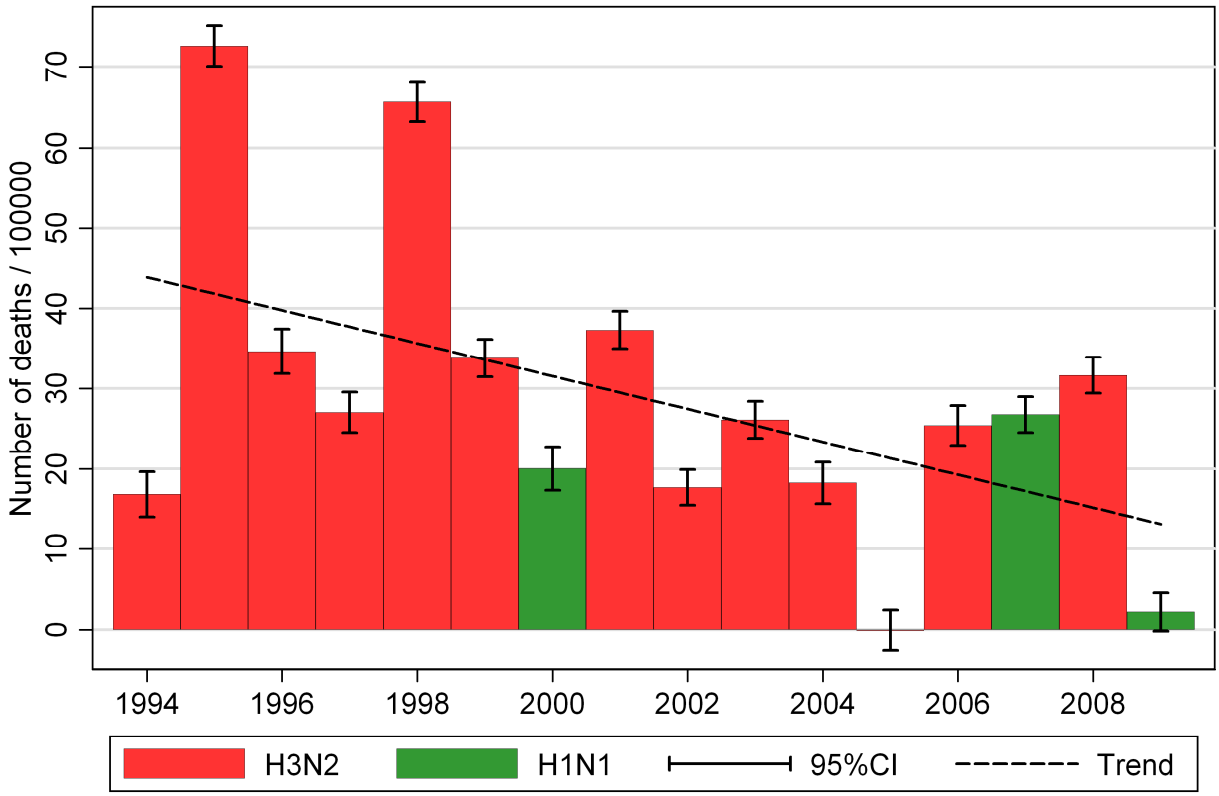


Table 1. The Danish population and dominating influenza virus, by season

Season[1]	Dominant virus	Population (100,000)				
		All ages	0-4 years	5-14 years	15-64 years	Aged 65
1994/95	H3N2	52.18	3.35	5.67	35.17	7.99
1995/96	H3N2	52.50	3.43	5.77	35.35	7.96
1996/97	H3N2	52.74	3.46	5.90	35.45	7.93
1997/98	H3N2	52.95	3.46	6.06	35.51	7.92
1998/99	H3N2	53.13	3.44	6.23	35.55	7.91
1999/00	H3N2	53.30	3.41	6.40	35.59	7.91
2000/01	H1N1	53.49	3.38	6.56	35.63	7.92
2001/02	H3N2	53.68	3.35	6.69	35.68	7.95
2002/03	H3N2	53.83	3.32	6.80	35.72	7.99
2003/04	H3N2	53.97	3.30	6.87	35.76	8.05
2004/05	H3N2	54.12	3.28	6.90	35.81	8.13
2005/06	H3N2	54.28	3.25	6.90	35.89	8.23
2006/07	H3N2	54.48	3.25	6.89	35.99	8.36
2007/08	H1N1	54.75	3.26	6.84	35.12	8.53
2008/09	H3N2	55.09	3.27	6.81	36.26	8.76
2009/10	H1N1[2]	55.35	3.26	6.75	36.30	9.04

1) Season: week 27 to week 26 the following year. 2) Pandemic influenza A(H1N1) 2009/10

Table 2. Excess mortality related to Influenza Like Illness, by season and age group

Season[1]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]
Age:	All ages		0-4 years		5-14 years		15-64 years		Aged 65	
1994/95	1812	34.73 (31.80;37.65)	20	5.94 (2.90;8.99)	7	1.21 (0.36;2.05)	-185	-5.26 (-6.97;-3.54)	1970	246.72 (229.23;264.21)
1995/96	5252	100.04 (97.22;102.86)	10	2.88 (0.51;5.25)	-12	-2.16 (-2.83;-1.49)	531	15.04 (13.26;16.82)	4723	593.64 (576.84;610.43)
1996/97	2555	48.43 (45.69;51.17)	13	3.69 (1.19;6.20)	10	1.64 (0.85;2.44)	285	8.05 (6.22;9.88)	2247	283.27 (267.05;299.49)
1997/98	2287	43.20 (40.65;45.76)	4	1.28 (-0.89;3.46)	-9	-1.51 (-2.23;-0.78)	364	10.26 (8.76;11.76)	1928	243.52 (227.85;259.19)
1998/99	4477	84.26 (81.81;86.71)	-3	-0.73 (-2.95;1.49)	19	2.97 (2.23;3.71)	478	13.43 (12.01;14.85)	3983	503.84 (488.70;518.98)
1999/00	2125	39.87 (37.55;42.19)	-10	-2.99 (-5.10;-0.88)	-5	-0.73 (-1.41;-0.05)	220	6.18 (4.63;7.73)	1920	242.87 (228.89;256.85)
2000/01	1706	31.89 (29.19;34.58)	38	11.19 (8.58;13.80)	1	0.11 (-0.60;0.81)	220	6.17 (4.67;7.67)	1447	182.75 (165.90;199.61)
2001/02	2615	48.71 (46.34;51.09)	19	5.71 (3.43;7.99)	-5	-0.68 (-1.24;-0.12)	304	8.51 (7.09;9.93)	2296	288.98 (274.30;303.65)
2002/03	1672	31.06 (28.72;33.41)	3	0.98 (-1.24;3.21)	-13	-1.87 (-2.45;-1.30)	159	4.45 (3.04;5.87)	1523	190.66 (176.19;205.12)
2003/04	1946	36.05 (33.74;38.36)	21	6.36 (4.00;8.72)	0	-0.04 (-0.67;0.60)	287	8.02 (6.65;9.39)	1638	203.58 (189.39;217.77)
2004/05	1414	26.13 (23.60;28.66)	-15	-4.61 (-6.98;-2.23)	-6	-0.89 (-1.45;-0.33)	225	6.30 (4.76;7.83)	1210	148.85 (133.49;164.22)
2005/06	306	5.63 (3.06;8.20)	-6	-1.72 (-3.97;0.53)	5	0.74 (0.21;1.27)	-59	-1.65 (-3-29;-0.01)	365	44.35 (28.99;59.70)
2006/07	1818	33.37 (30.86;35.87)	0	0.03 (-2.32;2.37)	5	0.71 (0.09;1.32)	287	10.74 (9.17;12.32)	1426	170.70 (155.89;185.51)
2007/08	1486	27.13 (24.84;29.42)	14	4.16 (1.97;6.36)	-1	-0.13 (-0.69;0.44)	397	10.98 (9.67;12.30)	1076	126.12 (112.56;139.69)
2008/09	2113	38.35 (36.09;40.62)	-11	-3.42 (-5.48;-1.35)	-4	-0.65 (-1.22;-0.08)	291	8.02 (6.76;9.28)	1838	209.83 (196.61;223.06)
2009/10	541	9.77 (7.41;12.14)	-3	-0.85 (-2.79;1.08)	10	1.50 (0.85;2.15)	55	1.50 (0.02;2.99)	479	53.01 (39.84;66.18)
Median	1882	35.39	4	1.13	-1	-0.08	286	8.02	1738	206.71

1) Season: week 27 to week 26 the following year. 2) Deaths per 100,000 per year

Table 3. Excess mortality associated to Influenza expressed by the influenza-index, by season and age group

Season[1]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]
Age:	All ages		0-4 years		5-14 years		15-64 years		Aged 65	
1994/95	877	16.82 (13.99;19.64)	-1	-0.22 (-2.96;2.51)	0	-0.00 (-0.81;0.80)	-233	-6.63 (-8.22;-5.03)	1111	139.16 (122.16;156.16)
1995/96	3810	72.58 (70.05;75.12)	7	2.14 (-0.15;4.43)	-10	-1.68 (-2.31;-1.05)	360	10.17 (8.72;11.62)	3453	434.03 (418.61;449.45)
1996/97	1827	34.64 (31.85;37.42)	3	0.74 (-1.72;3.19)	7	1.15 (0.37;1.92)	271	7.65 (5.92;9.39)	1546	194.95 (178.19;211.71)
1997/98	1432	27.04 (24.53;29.56)	0	-0.02 (-2.19;2.14)	-10	-1.60 (-2.30;-0.89)	276	7.77 (6.33;9.21)	1166	147.26 (131.79;162.73)
1998/99	3488	65.65 (63.23;68.08)	-11	-3.31 (-5.40;-1.22)	16	2.53 (1.77;3.28)	386	10.84 (9.45;12.24)	3098	391.91 (376.92;406.89)
1999/00	1802	33.80 (31.46;36.14)	-6	-1.83 (-3.94;0.28)	-3	-0.40 (-1.07;0.27)	158	4.43 (2.93;5.93)	1653	209.09 (194.87;223.31)
2000/01	1072	20.03 (17.32;22.74)	21	6.17 (2.77;9.57)	0	-0.03 (-0.74;0.67)	120	3.37 (1.92;4.82)	931	117.53 (100.49;134.57)
2001/02	2002	37.30 (34.99;39.62)	16	4.70 (2.47;6.93)	-2	-0.32 (0.87;0.24)	232	6.51 (5.18;7.83)	1756	221.02 (206.59;235.44)
2002/03	952	17.68 (15.46;19.90)	3	0.93 (-1.28;3.14)	-5	-0.74 (-1.43;-0.06)	122	3.41 (2.01;4.81)	832	104.20 (90.66;177.75)
2003/04	1409	26.10 (23.79;28.41)	17	5.12 (2.77;7.47)	1	0.18 (-0.43;0.79)	207	5.79 (4.45;7.13)	1183	147.07 (132.78;161.35)
2004/05	988	18.25 (15.66;20.84)	-13	-3.85 (-6.32;-1.37)	-7	-1.05 (-1.59;-0.52)	152	4.25 (2.69;5.81)	855	105.24 (89.47;212.01)
2005/06	-8	-0.14 (-2.68;2.40)	-6	-1.82 (-4.02;0.37)	5	0.68 (0.17;1.19)	-67	-1.86 (-3.59;-0.14)	61	7.37 (-7.60;22.33)
2006/07	1385	25.41 (22.93;27.90)	0	0.04 (-2.32;2.40)	3	0.48 (-0.17;1.13)	281	7.82 (6.31;9.33)	1100	131.60 (116.82;146.39)
2007/08	1465	26.76 (24.51;29.00)	17	5.20 (3.08;7.31)	-1	-0.21 (-0.75;0.34)	287	7.95 (6.66;9.24)	1162	136.23 (122.91;149.56)
2008/09	1744	31.65 (29.41;33.89)	-10	-3.19 (-5.23;-1.15)	-4	-0.57 (-1.13;-0.00)	215	5.92 (4.68;7.15)	1543	176.22 (163.11;189.33)
2009/10	121	2.19 (-0.19;4.57)	-2	-0.64 (-2-54;1.26)	8	1.17 (0.52;1.83)	-11	-0.29 (-1.72;1.14)	126	13.93 (0.58;27.29)
Median	1420	26.43	0	0.01	-1	-0.12	211	5.86	1164	143.11

1) Season: week 27 to week 26 the following year. 2) Deaths per 100,000 per year

Table 4. Excess mortality associated to extreme ambient temperatures, by season and age group

Season[1]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]	Death	Mortality[2]
Age:	All ages		0-4 years		5-14 years		15-64 years		Aged 65	
1994/95	7	0.14 (-2.97;3.24)	-1	-0.19 (-3.88;3.49)	-2	-0.36 (-1.30;0.57)	50	1.42 (-0.48;3.32)	-40	-5.03 (-23.47;13.41)
1995/96	273	5.20 (1.88;8.52)	5	1.36 (-1.37;4.09)	0	0.07 (-0.61;0.74)	85	2.39 (0.22;4.57)	183	23.05 (3.43;42.67)
1996/97	86	1.63 (-1.54;4.80)	2	0.56 (-2.39;3.51)	-2	-0.34 (-1.27;0.58)	70	1.99 (-0.26;4.24)	16	1.99 (-16.46;20.44)
1997/98	117	2.22 (-0.70;5.13)	1	0.21 (-2.29;2.71)	-1	-0.24 (-1.09;0.61)	56	1.58 (-0.17;3.34)	62	7.80 (-9.98;25.59)
1998/99	212	2.28 (-0.49;5.06)	3	0.94 (-1.71;3.60)	-1	-0.17 (-1.09;0.74)	56	1.59 (-0.04;3.21)	63	7.93 (-9.16;25.02)
1999/00	-17	-0.32 (-2.91;2.26)	-1	-0.28 (-2.78;2.22)	-2	-0.34 (-1.14;0.46)	37	1.03 (-0.82;2.87)	-51	-6.40 (-21.66;8.85)
2000/01	-162	-3.02 (-6.18;0.13)	-2	-0.67 (-3.88;2.53)	-3	-0.45 (-1.31;0.41)	46	1.29 (-0.43;3.01)	-203	-25.57 (-45.35;-5.79)
2001/02	-139	-2.58 (-5.30;0.13)	-4	-1.13 (-3.95;1.69)	-2	-0.29 (-0.92;0.35)	32	0.90 (-0.80;2.59)	-165	-20.76 (-37.40;-4.12)
2002/03	241	4.47 (1.81;7.14)	4	1.13 (-1.55;3.81)	0	-0.05 (-0.69;0.59)	69	1.94 (0.29;3.60)	167	21.03 (4.72;37.33)
2003/04	64	1.19 (-1.30;3.68)	1	0.25 (-2.53;3.02)	-2	-0.26 (-1.00;0.48)	56	1.56 (0.09;3.04)	9	1.15 (-14.18;16.48)
2004/05	14	0.25 (-2.67;3.17)	2	0.52 (-2.30;3.34)	-3	-0.44 (-1.06;0.19)	62	1.72 (-0.04;3.48)	-47	-5.77 (-23.54;12.00)
2005/06	174	3.21 (0.13;6.29)	4	1.25 (-1.48;3.97)	0	-0.03 (-0.65;0.58)	74	2.05 (0.04;4.07)	97	11.77 (-6.50;30.04)
2006/07	-135	-2.47 (-5.32;0.38)	-5	-1.44 (-4.16;1.28)	-3	-0.39 (-1.08;0.30)	50	1.39 (-0.47;3.25)	-177	-21.22 (-37.93;-4.52)
2007/08	-146	-2.66 (-5.27;-0.05)	-3	-0.89 (-3.47;1.68)	-3	-0.39 (-1.04;0.26)	48	1.33 (-0.17;2.83)	-188	-22.06 (-37.51;-6.61)
2008/09	-8	-0.14 (-2.79;2.50)	0	-0.12 (-2.60;2.36)	-2	-0.23 (-0.89;043)	32	0.89 (-0.54;2.33)	-38	-4.39 (-19.91;11.13)
2009/10	164	2.97 (0.32;5.62)	2	0.66 (-1.50;2.81)	0	0.06 (-0.71;0.83)	61	1.67 (-0.01;3.36)	101	11.17 (-3.55;25.88)
Median	39	0.72	1	0.23	-2	-0.27	56	1.57	-15	-1.62

1) Season: week 27 to week 26 the following year. 2) Deaths per 100,000 per year

Table 5. Temperature associated mortality differentiated on summer and winter, all ages

Season[1]	Summer (week 14 to 39)						Winter (week 40 to 13)					
	Cold			Warm			Cold			Warm		
	Death	Mortality[2]	Weeks	Death	Mortality[2]	Weeks	Death	Mortality[2]	Weeks	Death	Mortality[2]	Weeks
1994/95	-30	-0.58 (-3.78;2.62)	7	67	1.29 (-1.87;4.45)	5	84	1.62 (-1.56;4.79)	4	-114	-2.19 (-5.38;1.00)	15
1995/96	-46	-0.88 (-4.23;2.48)	10	44	0.84 (-2.52;4.19)	6	313	5.97 (2.62;9.33)	17	-38	-0.73 (-4.09;2.62)	5
1996/97	-79	-1.50 (-4.74;1.75)	14	39	0.75 (-2.52;4.01)	6	199	3.78 (0.54;7.01)	12	-74	-1.40 (-4.66;1.87)	7
1997/98	-6	-0.11 (-3.11;2.88)	2	94	1.78 (-1.18;4.74)	11	116	2.19 (-0.78;5.15)	6	-87	-1.64 (-4.63;1.35)	7
1998/99	-65	-1.22 (-4.06;1.63)	15	-2	-0.03 (-2.89;2.82)	2	215	4.05 (1.22;6.87)	11	-28	-0.52 (-3.36;2.32)	5
1999/00	-22	-0.41 (-3.07;2.26)	3	72	1.36 (-1.26;3.98)	9	20	0.37 (2.30;3.04)	2	-88	-1.65 (-4.30;1.01)	9
2000/01	-87	-1.63 (-4.84;1.57)	15	0	0.00 (-3.24;3.24)	0	86	1.61 (1.62;4.83)	6	-160	-3.00 (-6.20;0.20)	14
2001/02	-19	-0.35 (-3.13;2.43)	6	50	0.94 (-1.83;3.71)	11	7	0.12 (-2.67;2.91)	1	177	-3.29 (-6.03;-0.56)	14
2002/03	-28	-0.51 (-3.23;2.21)	4	62	1.15 (-1.57;3.87)	9	235	4.36 (1.65;7.07)	15	-29	-0.53 (-3.27;2.21)	3
2003/04	-41	-0.76 (-3.36;1.84)	6	61	1.14 (-1.47;3.75)	9	124	2.30 (-0.29;4.89)	8	-80	-1.49 (-4.06;1.09)	6
2004/05	-105	-1.95 (-4.91;1.02)	15	20	0.37 (-2.64;3.38)	3	154	2.84 (-0.15;5.84)	9	-55	-1.01 (-4.01;1.98)	3
2005/06	-82	-1.51 (-4.60;1.58)	12	0	0.00 (-3.11;3.11)	0	286	5.27 (2.17;8.37)	14	-30	-0.55 (-3.65;2.56)	3
2006/07	-10	-0.18 (-3.11;2.76)	1	107	1.97 (-0.91;4.85)	15	0	0.00 (-2.94;2.94)	0	-232	-4.26 (-7.18;-1.35)	17
2007/08	-62	-1.14 (-3.78;1.51)	12	23	0.41 (-2.25;3.02)	5	83	1.51 (-1.15;4.17)	7	-189	-3.45 (-6.11;-0.79)	15
2008/09	-28	-0.51 (-3.21;2.18)	7	38	0.70 (-1.98;3.38)	6	53	0.96 (-1.73;3.65)	4	-71	-1.30 (-3.99;1.40)	10
2009/10	-22	-0.40 (-3.10;2.30)	7	56	1.02 (-1.67;3.70)	9	179	3.23 (0.05;5.91)	11	-49	-0.88 (-3.58;1.83)	6
Median	-36	-0.67	7	47	0.89	6	119	2.24	8	-77	-1	7

1) Season: week 27 to week 26 the following year. 2) Deaths per 100,000 per year

Table 6. Mortality related to influenza

Country	Period	Age group	Mortality per 100,000	Method	Reference
West Germany Germany	1984/85-1994/95 1990/91-2000/01	All	16.1 (range: 2.2;35.7) 17.4 (range: 5.9;44.2)	All cause	Zucs 2005
USA	1972/73-2002/03	All	65.0 (range: 0;134.2) 72.4 (range11.7;144.7)	All cause	Thompson 2009
Canada	1997-2000 2000-2004	All	15,6 5.8 (vaccination)	All cause	Kwong 2008
Italy	1969-2001	All	23.4 (H3N2) / 7.4 (H1N1)	All cause	Rizzo 2007
Canada	1989/90-1998/99	All	13.1	All cause	Schanzer 2007
South Africa USA	1998-2005 1997/98-2004/05	65+	340 112	All cause	Cohen 2010
Czech Republic	1982/83-1999/00	65+	26.0 (range: -8.9;60.4)	All cause	Kyncl 2005
Netherlands	1992-1996 1996-2003	65+	131 (95% CI: 123-139) 105 (95% CI: 99-111) (vaccination)	All cause	Jansen 2008
Hong Kong	1996-1999	65+	93.2 (95% CI: 78.4-107.7) 136.1 (95% CI: 83.7-188.4)	All cause	Wong 2004
Portugal	2008/09	65+	18	All cause	Nogueira 2009
Switzerland	1969/70-1998/99 1988/89-1998/99	60+	67.2 (range: 20.9;209,5) 152.8 (range: 66.3;293.3) 69.5 (range: 32.6;234,5) 187.1 (range: 121.0;356.0) 115.3 (range: 60.6;226.9)	All cause	Brinkhof 2006
Netherlands	1967-1989	60+	82	All cause	Sprenger 1993
USA	1976/77-2006/07	All	9.0 (range: 1.4;16.7) 2.4 (range: 0.4;5.1)	RC PI	MMWR 2010
Italy	1969-2001	All	4.5 (H3N2) / 0.8 (H1N1)	PI	Rizzo 2007
USA France Australia	1972-1997	All	2.6 (range: 0;6.3) 3.9 (range: 0;18.3) 1.3 (range: 0;7.5)	PI	Viboud 2004
South Africa USA	1998-2005 1997/98-2004/05	65+	42 22	PI	Cohen 2010
Hong Kong	1996-1999	65+	16.7 (95% CI: 9.8-23.7) 39.3 (95% CI: 21.4-57.3)	PI	Wong 2004
France	1984-2004	65+	1.4 (range: 0;9.4)	PI	Denoeud 2007

RC: Respiratory and circulatory cause's incl. pneumonia and influenza. Vaccination: After introduction of vaccination programme

2.3. Mortality in The Netherlands

Understanding trends in mortality: mortality attributable to common infections

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SUMMARY
To understand trends in mortality we analysed which common infections are associated with overall mortality in the Netherlands in the elderly. On weekly time series (1999-2007) we used Poisson regression models to characterize the association of total death counts with trends in common seasonal viruses and bacteria for which robust weekly laboratory surveillance data were available (influenza A and influenza B, RSV, parainfluenza, enterovirus, rotavirus, norovirus, *Campylobacter* and *Salmonella*). We adjusted for extreme outdoor temperatures and we stratified by age. Besides influenza A and RSV, also influenza B, parainfluenza and norovirus contribute substantially to mortality. Influenza A and RSV was significantly associated with mortality in all elderly; influenza B, and parainfluenza additionally in those ages 75+ years, and also norovirus in those aged 85+ years. Influenza A and influenza B were associated with mortality without delay, while other viruses was associated with mortality 2-4 weeks later. The proportion of deaths attributable to seasonal viruses was: 6.9% (85+ years); 4.7% (75-84 years); 1.5% (65-74years). The mortality attributable to influenza alone ranged from 2% in the eldest down to 0.9% in the youngest group.
The number of viruses associated with elderly mortality increases with increasing age. Surprisingly, influenza A was usually, but not exclusively, associated with the highest numbers of deaths; occasionally RSV or influenza B had a greater impact on elderly mortality.

INTRODUCTION
Although winter seasonality in overall death counts is largely attributed to influenza and sometimes cold temperatures, the contribution of other common seasonal viruses and bacteria to deaths in the elderly is not entirely clear. In this study we therefore analysed which common infections are associated with overall mortality in the Netherlands.

METHODS

Per age group we modeled time series of weekly overall number of deaths (outcome variable) depending on: common seasonal viruses and bacteria at the population level, temperature, and baseline cyclical (i.e. seasonal) trends. We used weekly time series (1999-2007) from 3 data sources:

1) Overall Mortality data

Mortality statistics originate from Statistics Netherlands (CBS) and cover the total Dutch population (16.3 million) between 1999 and 2007. As numbers of deaths in children are small, we restricted analyses to the elderly population, aggregating numbers of deaths by 10 year age groups (65-74, 75-84, and 85 and older). Yearly population size by age was also available from Statistics Netherlands (CBS).

2) Data on viruses and bacteria from laboratory surveillance

For viruses we used time series of influenza A and influenza B, RSV, parainfluenza, enterovirus, and rotavirus, available from laboratory surveillance for 1999-2007 [1] ('Weekly Sentinel Surveillance System' of the Dutch Working Group on Clinical Virology), and norovirus trends from the norovirus outbreak surveillance system. For bacteria we included time series of *Campylobacter* and *Salmonella* available from the Laboratory Surveillance of Infections. The time series are considered representative for the total Dutch population[1], although the coverage varies by pathogen, and counts are not available by age group but with probable overrepresentation of young children.

3) Temperature

Daily mean temperatures were downloaded from the website of the Royal Netherlands Meteorological Institute (KNMI), and then were aggregated to the weekly mean.

Statistical analyses

We used poisson regression models to relate the overall mortality to laboratory counts of pathogens. We used the identity link function because we expect that the association between the number of pathogens and the expected number of deaths is additive instead of multiplicative, and a scale parameter was added to take the over-dispersion into account. We included baseline periodic trends (sine and cosine terms) since many health variables show systematic variation over the course of a year even if these variables are not causally related[2]. We further adjusted models for average daily outdoor temperatures by including two temperature variables: one for low temperatures, given by max(0, 5-T), the other for high temperatures, given by max(0, T-17). Between 5 ºC and 17 ºC no temperature effect is expected[3].We also evaluated the association with the lagged values of the pathogens (up to 4 weeks backwards in time).

The following regression model was used:

$$\text{Deaths}_t \sim \text{Poisson}(\lambda_t)$$

$$\lambda_t = \beta_0 + \beta_1 t + \beta_2 \sin(2\pi t/52) + \beta_3 \cos(2\pi t/52) + \beta_4 \max(0, 5 - T_t) + \beta_5 \max(0, T_t - 17) + \beta_6 P_{1,(t-lagP1)} + \beta_7 P_{2,(t-lagP2)} + \ldots + \beta_m P_{k,(t-lagPk)}$$

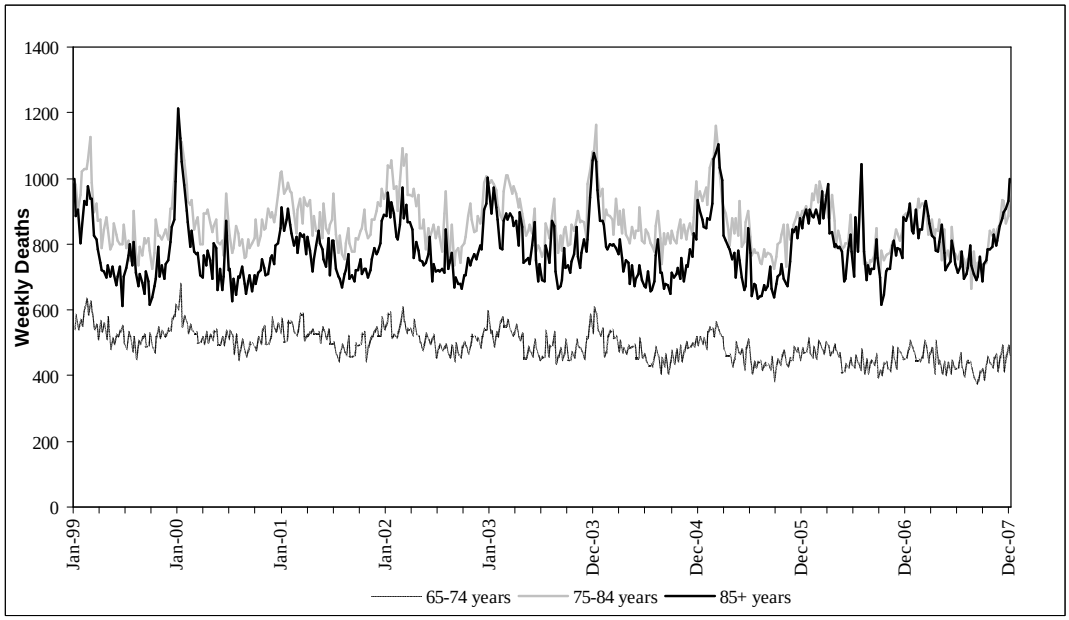
In this equation β_0 is the regression parameter associated with the baseline number of deaths, β_1 the parameter associated with a linear trend in time, β_2 and β_3 the parameters associated with the periodic time trends, and β_4 and β_5 the parameters associated with low and high temperature effects. Parameters β_6, β_7, ..., β_m are the parameters of interest, describing the association between the lagged number of pathogens P_1, P_2, ..., P_k and the expected number of deaths.

RESULTS

Characteristics

The mean weekly number of deaths varied from 490 to 865 deaths in the different age groups, and also varied largely by season, especially in the two oldest age groups (fig 1). Laboratory reports of the different pathogens varied from an average of 2 to 65 per week with large inter quartile ranges due to the strong seasonality in their prevalence.

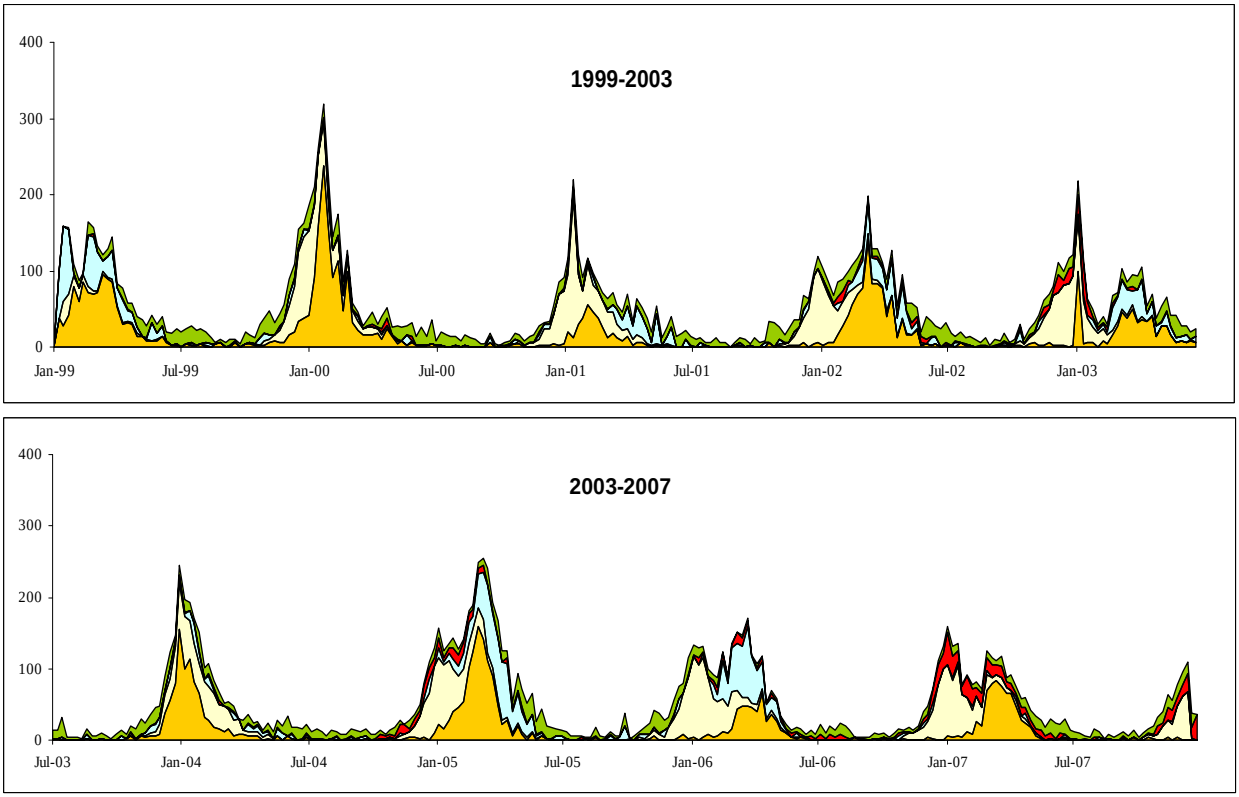
Figure 1. Overall weekly mortality by elderly age group 1999-2007



Model results

Influenza A and RSV was significantly associated with mortality in all elderly age groups, while influenza B and parainfluenza associated significantly with mortality in the oldest two age groups (75-84 and 85+ years). Additionally, norovirus activity was a significant predictor of mortality in the oldest individuals (85+ years). None of the considered bacteria were significant in any of the age groups. In the final models we adjusted for high temperature only, as low temperature was not significantly predictive of mortality in any of the age groups. The trend in the numbers of deaths attributable to different pathogens in the oldest age group (85+) is shown in figure 2.

Fig.2. Weekly deaths attributable to respiratory and gastro-intestinal viruses in individuals aged 85 years and older (stacked).



(■ influenza A, ■ RSV, ■ influenza B, ■ norovirus, ■ parainfluenza)

Delay in mortality and model fit

Influenza showed the best fit in all age groups when it was directly associated with mortality (i.e. without delay in subsequent mortality), while RSV virus showed an optimal fit when deaths were lagged 2-3 weeks after RSV activity. For parainfluenza the optimal lag varied by age, with a longer lag in the oldest age group (3 weeks, see table 2). Also norovirus was associated with subsequent mortality 4 weeks later in the eldest age group. The fit of the models seemed adequate (visual inspection), but with seemingly slight autocorrelation remaining in the distribution of the residuals (see fig 2 for the oldest individuals), for which unknown variables may be accountable. Observed winter peaks were sometimes slightly more peaky than our models predicted, but also other seasons sometimes had small proportions of mortality left unexplained by our models.

Estimated numbers of attributable deaths

In the oldest age group (85+ years) 6.9% of all mortality was attributed to multiple winter viruses (influenza A&B, RSV, parainfluenza, norovirus) during the total study period. This proportion decreased with decreasing age (75-84 years:4.7%; 65-74years:1.5%), also because with decreasing age less viruses were significant predictors of death (but always including influenza A and RSV. The absolute numbers of deaths associated with all viruses varied by season with the following minimum and maximum estimates for all elderly in the Netherlands: 320-613 (65-74 year olds); 1,647-2,775 (75-84 year olds), and 2,170-3,729 (85+ years) (table 1).

Table 1. Estimated numbers of deaths attributable to viruses and high temperature by age and season (each july-june).

SEASON	1999/2000		2000/2001		2001/2002		2002/2003		2003/2004		2004/2005		2005/2006		2006/2007	
	absolute	rate*	absolute	rate*	absolute	rate*	absolute	rate*	absolute	rate*	absolute	rate*	absolute	rate*	absolute	rate*
65-74 years																
Influenza A	395	*0.3*	107	*0.1*	265	*0.2*	171	*0.1*	257	*0.2*	315	*0.3*	142	*0.1*	190	*0.1*
RSV	218	*0.2*	213	*0.2*	159	*0.1*	182	*0.1*	176	*0.1*	205	*0.2*	233	*0.2*	203	*0.2*
75-84 years																
Influenza A	1147	*1.6*	311	*0.4*	770	*1.0*	498	*0.7*	746	*1.0*	916	*1.2*	413	*0.5*	552	*0.7*
RSV	672	*0.9*	654	*0.9*	490	*0.7*	559	*0.7*	542	*0.7*	631	*0.8*	718	*0.9*	626	*0.8*
Influenza B	100	*0.1*	266	*0.4*	378	*0.5*	347	*0.5*	201	*0.3*	702	*0.9*	586	*0.7*	54	*0.1*
Parainfluenza	682	*0.9*	449	*0.6*	573	*0.8*	496	*0.7*	505	*0.7*	527	*0.7*	372	*0.5*	415	*0.5*
Temp. = 17°C	527	*0.7*	185	*0.3*	447	*0.6*	491	*0.6*	507	*0.7*	489	*0.6*	369	*0.5*	749	*0.9*
85+ years																
Influenza A	1386	*6.3*	378	*1.7*	930	*4.1*	603	*2.6*	905	*3.9*	1106	*4.7*	502	*2.1*	668	*2.7*
RSV	946	*4.3*	921	*4.1*	690	*3.0*	787	*3.4*	764	*3.3*	888	*3.8*	1010	*4.2*	881	*3.5*
Influenza B	123	*0.6*	326	*1.4*	463	*2.0*	426	*1.8*	246	*1.1*	861	*3.7*	719	*3.0*	66	*0.3*
Parainfluenza	781	*3.5*	512	*2.3*	614	*2.7*	551	*2.4*	580	*2.5*	599	*2.6*	401	*1.7*	470	*1.9*
Norovirus outbreak	50	*0.2*	33	*0.1*	107	*0.5*	243	*1.1*	50	*0.2*	276	*1.2*	169	*0.7*	480	*1.9*
Temp. = 17°C	715	*3.2*	251	*1.1*	607	*2.7*	667	*2.9*	690	*3.0*	665	*2.9*	502	*2.1*	1017	*4.1*

* per 1000 individuals

CONCLUSION

This study shows that seasonal mortality in the elderly seems attributable to multiple viruses: influenza A, RSV, influenza B, norovirus and parainfluenza. Together, these viruses were associated with up to 6.9% of all deaths in the eldest age group of 85 years and older. Influenza A wasn't always associated with the highest numbers of deaths; sometimes RSV and influenza B had a greater impact on elderly mortality. The number of viruses that contributed to overall mortality decreased with decreasing age in the elderly population (aged 65 years and older), but always included influenza A and RSV. Cold weather wasn't significantly associated with increased winter mortality in Dutch elderly.

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2.4. Mortality in the U.K.

Modeling death registrations in England to enable prospective detection of excess deaths

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Background

Various recent public health threats due to emerging or re-emerging communicable diseases (e.g. avian influenza, pandemic influenza) or environmental factors (climate change with periods of extreme heat or cold and pollution) have reinforced the need for regular monitoring of mortality (1).

Death certification alone it not timely enough and too non-specific to accurately attribute the etiology of excess death to one or the other factors and alternative methods have been developed to rapidly estimate excess deaths (2-5).

An excess of mortality is observed when mortality increases above expected seasonal cycles. This has been described in numerous retrospective studies during influenza epidemic(6-8), heat waves(9-12) and cold snaps(13;14), but also for other respiratory(15-17) or enteric viruses(18) and peak of pollution(19;20).
Influenza related mortality has been estimated for several decades using methods developed by Serfling (7;21-23). Serfling related methods attribute any excess above the seasonal cyclical variations to influenza. These methods are simple and robust, but ignore the influence of other important factors, in particular temperature. Regression models have been applied to historical time series to estimate the contribution of various factors to morbidity and mortality(17;24;25). Regression models, could also be used for the prospective monitoring of the main causes of mortality variation and to define thresholds in order to detect various types of excess mortality.

The objectives of the study were to validate a new method for the prospective weekly surveillance of mortality in England:

16. Modelling weekly death occurences with a multivariable regression model using weekly available influenza and temperature data.
17. Using the model to prospectively detect and measure excess death occurrences and death registrations due to influenza, extreme temperature and other unknown factors, in various subgroups of the population: by region, by age group and by broad cause of death.

MATERIALS AND METHODS

General principle

To weekly detect and measure an excess of deaths in a specific population, the observed number of deaths for one specific week must be compared to the expected number of deaths that same week if no particular factor increasing mortality was present. This expected number of deaths can be modeled from the historical time series with a regression approach estimating and controlling the main factors increasing mortality (influenza and extreme temperature). The model coefficients can be used to estimate the expected number of deaths in the absence of influenza or extreme temperature. If the observed number of death is above a threshold defined according to the variance of the series controlled for influenza and mortality, it is considered in excess.

Data sources and constitution of the time series

ONS provided data on individual deaths registered between 1993 and 2003 in England. The Health Protection Agency provided the weekly number of laboratory confirmed influenza cases identified through the routine influenza laboratory surveillance system in England. The Met Office provided daily temperature data recorded in one pre-selected met station in the main town of the nine Government Office Regions of England (GOR). The temperature of Heathrow was used as a proxy indicator of the temperature when analysing data for all England.

Mortality data were aggregated by week of death occurrence and week of death registration (from Monday to Sunday) for all England, by age group (below one year, 1 to 4, 5 to 14, 15 to 44, 45 to 64, 65 to 74, 75 to 84 and above 84 years), by the nine GOR and by underlying cause of death grouped into 9 disease categories (see appendix). The underlying cause of death was defined, according to the *International Classification of Diseases*, Ninth and Tenth Revision (ICD 9 and 10), as the cause that initiates the chain of events leading ultimately to death. A total of 26 series by week of registration and 26 series by week of death occurrence were computed and modeled using identical principles.

Weather indicator

We first modeled a baseline temperature time series representing cyclical seasonal temperature variation by a sine curve, using a linear regression including sine terms (Figure 1). Extreme cold and heat were defined by temperature variation respectively departing from the lowest and highest level of the baseline temperature.

For the final model, a three-week moving average of the daily maximal temperature was the indicator that gave the best model fit across the series, chosen from various combinations of indicators (weekly means, minimal, maximal temperature, humidity and atmospheric pressure) and length of moving average. As the relationship between number of deaths and temperature is not linear (9;26), a linear spline function was used to model the relationship between the number of deaths and the temperature with 4 segments. The four spline variables were used as additive terms in the model. The regression coefficients associated with the upper and lower spline variables represented the influence of extreme cold and heat on mortality.

The model

We computed the expected number of death occurrences / registrations for any week under study with a generalized linear model of the Poisson family fitted using maximum likelihood estimation on the 260 previous weeks (5 years). The model and its output (Expected number of deaths and excess deaths) were iteratively and

prospectively recomputed for each week between Monday 5th of January 1998 and Sunday 28th of September 2003: a period corresponding to 300 weeks. In order to give an example of the model output, the same model was also fitted once on the available data set (1993 to 2003 in England).
The explanatory variables were:
- the week number representing the trend over time, starting from week one 1993 (wknum)
- influenza A weekly number of laboratory confirmed cases (fluA). Influenza B was not a significant factor influencing mortality in our series and was not introduced in the model.
- three week moving average of the weekly average of the maximal daily temperature expressed as a linear spline by 4 variables (temp1 to temp4).
- a dichotomized variable created to differentiate cause of death coded with ICD9 before 2001 and cause of death coded with ICD10 from 2001[28].

A preliminary model was computed from these variables. Autocorrelation remaining in the residual was modeled with one and two-week lag terms using a simple regression. In order to improve the validity of the estimation of the standard error of the model and its parameters, the remaining autocorrelation was then introduced into the initial model, as a new explanatory variable representing the autocorrelation not already included in the influenza A and temperature variables.
The fit of the models was assessed through visual examination of the series. We also estimated the proportion of the variance explained by the model by calculating the squared multiple correlation coefficients (R^2) between the observed and the expected number of death occurrences / registrations for all the series over the study period(30). Significance of the remaining autocorrelation was also tested(31).

Disentangling causes of excess death

Partial regression coefficients (β_0 to $\beta 8$) represent the contribution of each of these factors to the weekly mortality. The number of deaths attributable to a specific factor (trend, seasonal cyclical variation, temperature variation departing from seasonal cyclical variation, influenza), was obtained by differentiation between the output of the model fitted on the real data (mortality and explanatory variables) and the output of the same model (same coefficients) using explanatory variable respectively set to baseline values. As no other explanatory variables were annually cyclical, the cyclical seasonal variation of the temperature (excluding extreme temperature) was used for modeling the seasonal cyclical variations in the number of deaths, without establishing a particular causal link between the 2 cycles.
Any death attributed by the model to influenza is considered in excess. Any death positively attributed by the model to temperature departing from the highest and lowest cyclical seasonal temperature variation (Figure 1), is also considered in excess. Positive differences between the model and the observed number of deaths are attributed to an unknown cause of excess death.

Prediction interval and detection threshold

We calculated a 95 percent prediction interval around the expected number of deaths using the variance of the final model and the variance of the residuals. To decrease the influence of outliers, we removed residual values when the standardized residuals were beyond two standard deviations.

A week with an excess of deaths is detected when the number of cases is above a threshold computed from the 95% prediction interval applied to specific number of deaths computed from the model.
We could then detect an:

- Excess above a cyclical seasonality (Constant + trend + modeled cyclical season)
- Excess above any temperature variation (Constant + trend + temperature variation)
- Excess above any temperature variation and influenza activity (Constant + trend + temperature + influenza)
- Excess above the full model.

Statistical analyses were performed using Stata 8.2

RESULTS

Only a selection of visual examples is provided here to illustrate the possible usefulness of the model for a prospective monitoring. We emphasize the possibility for early detection rather than a retrospective quantification of the impact of environmental factor possibly influencing mortality.

Model fit

The models visually fitted well the general trends in all the mortality series (sample of series provided in Figure 2). The proportion of the variance explained by the final model (R^2) varied between 72 and 89% when applied at national or regional level. The R^2 was ≥76% in series that were likely to be strongly influenced by influenza or temperature (age groups ≥ 65 years, deaths by respiratory or cardio-vascular diseases). For other groups (e.g. other diseases and age groups below 45 years), despite a good visual fit on the general trends, the R^2 decreased as low as 3% as the week-to-week random variation became close to the average number of deaths (Table 1).

Component of excess of death

To better illustrate how components of mortality are attributed, results for London when the model is fitted on 10 year historical data are presented (Figure 3). Influenza was the main contributing component of the winter peaks (winters 1993/94, 1998/99 and 1999/2000. Major mortality peaks related to extreme cold were visible, alone or concomitant to influenza peaks (winters 1996/97, 1997/98, 2000/01 and 2001/02). Peaks related to extreme heat are visible in summer 1995, 1997 and 2003. The number of deaths observed is often lower than the prediction after high winter mortality peaks, corresponding to a harvesting effect (1996, 1997, 2000, and 2001). Winter peaks, unexplained or only partially explained by influenza or cold are also visible (winter 1994/5, 1999/2000 and 2002/03).

Surveillance results

The results virtually correspond to 5 years of weekly surveillance of death registrations and death occurrences in 26 subgroups of population. Weekly measurement of the impact of cyclical seasonality, extreme temperature and influenza was achieved, even in those series with a low number of weekly deaths. Significant excess deaths were detected according to thresholds defined by the model (above a cyclical seasonality, above temperature variation, above temperature and influenza and above the complete model) **(**Figure 4**)**. Any excess above the complete model corresponds to deaths not explained by the model and is due to other unknown causes or to random variation. As an example, in using the total number of death in England, during the study period of 300 weeks, 41 weeks had an excess above temperature variation threshold and 23 had an excess above temperature variation and influenza activity threshold.

DISCUSSION

Our study suggests that a simple and robust regression model can be applied weekly to detect and quantify excess deaths in variety of population subgroups and to attribute the excess to the main factors responsible for short term death variations (extreme temperature, influenza and other causes).

Limitations

Influenza strain (related to variation of the influenza case fatality) and other factor known to trigger death (other viruses, pollution indicators) were not included in the model. This could be the reason for the unexplained peak of death visible in figure 3 although the model still explained most of the short term variations. The model has actually been designed for weekly surveillance. To be functional, explanatory variables (influenza data and temperature and possibly other) must also be available on a weekly basis at national and regional level.
The choice of one single weather station to represent the average temperature in all the country may not be appropriate in countries with large climatic variations. Regional influenza data were also not available and the total number of laboratory confirmed cases in England was used to represent influenza A activity, whereas influenza activity may vary temporally from one region the other. These simplifications may decrease the accuracy of the model estimates but do facilitate its implementation as a routine monitoring system. Using a cycle in the model to control for cyclical variation is valid only if we are certain that no other variable is collinear with a seasonal cyclical variation. De-seasonalised mortality should be modelled instead to ensure that only unexpected variations above cyclical seasonality are modeled.

Effect of extreme temperatures and Influenza

The effect of heat waves on mortality have been extensively described in various countries and is also captured by our model. However, the effect of cold is less studied. Our analysis on English data shows that the effect of extreme cold can be substantial, alone or at the same time as influenza epidemic (in our data sets, there was no statistically significant correlation or interaction between extreme cold and influenza). The effect of Influenza and temperature variation cannot be studied separately. The effect of temperature variations must be controlled in order to better study the effect of influenza or other factors on winter mortality, and inversely. Unlike Serfling-based seasonal regressions, our model can weekly provide an estimation of the effect of influenza on the number of deaths, adjusted for the effect of cold weather and without the effect of possible other emerging causes.

Other factors affecting deaths

Being able to distinguish excess deaths after adjustment and control for temperature variation and influenza activity also enables the detection and the measurement of excess death due to other possible causes, on a weekly basis and possibly trigger investigation of suspicious peaks. If data on other viruses or pollution are available on a weekly basis, these could be integrated to the model to also routinely measure their specific impact.

CONCLUSIONS

Our study suggests that a simple and robust regression model can be used on a weekly basis to detect and measure excess deaths, across various population groups. The model can attribute excess deaths to extreme temperatures, influenza, or other unknown causes. Alerts should be validated according to the context. Validated alerts need to be rapidly investigated by in-depth analysis and field studies. The implementation of mortality monitoring as we outline will require appropriate means and human resources.

Acknowledgment: We thank Clare Griffiths and Sue Davies from the Office for National Statistics in London, as well as Dr William Bird and Mark Gibbs from the UK Met Office for their contribution to the study.

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Tables and figures:

Table 1
Squared multiple correlation coefficients (R^2) calculated between expected and observed weekly number of death occurrences and registrations by population subgroups in England, 1998 to 2003.

Population subgroups	Number of deaths during the first week of August 2002*	R^2 for death occurrence series	R^2 for death registration series
Total England	9728	0.89	0.81
By region		0.79 to 0.86	0.72 to 0.80
By underlying cause of death			
Cardio - vascular	3136	0.96	0.86
Respiratory	1131	0.84	0.94
Neurological	178	0.63	0.61
Infectious neurological	7	0.39	0.34
Gastro-intestinal	428	0.62	0.44
Infectious gastrointestinal	16	0.53	0.54
Renal	139	0.42	0.40
Other infectious	48	0.80	0.78
By age group			
under 1 year	56	0.22	0.16
1 to 4	6	0.25	0.25
5 to 14	20	0.03	0.07
15 to 44	366	0.45	0.08
45 to 64	1258	0.69	0.55
65 to 74	1753	0.88	0.78
75 to 84	3263	0.87	0.81
85 and over	3006	0.89	0.86

Figure 1: Temperature variations
Weekly maximum temperature and modeling of cyclical seasonality, London, England, 1993 to 2003.

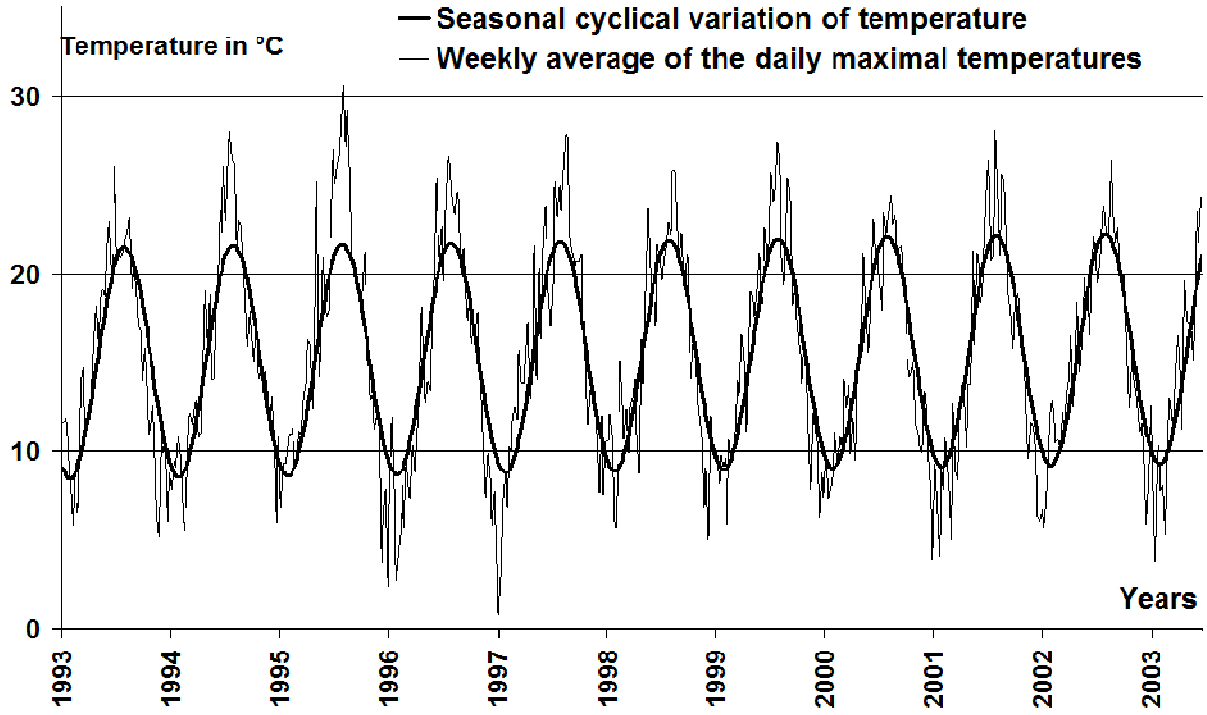


Figure 2: Modeling death occurrences using death registrations
Observed weekly number of death occurrences and expected number of death registrations, for cardio-vascular and infectious neurological diseases and for 1 to 4 years age group, England, 1998 to 2003.

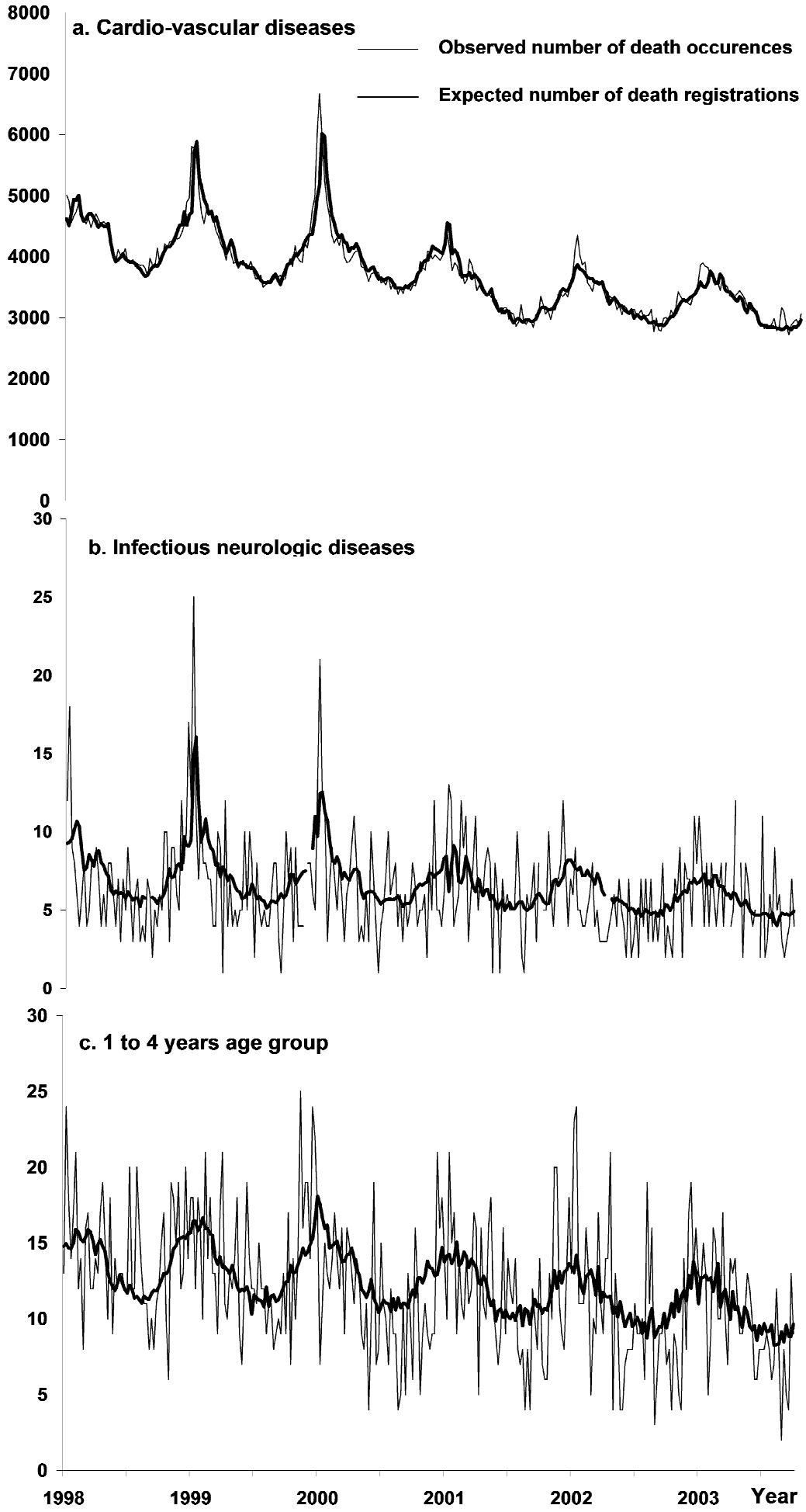

a. Cardio-vascular diseases
Observed number of death occurences
Expected number of death registrations
8000
7000
6000
5000
4000
3000
2000
1000
0
b. Infectious neurologic diseases
30
25
20
15
10
5
0
c. 1 to 4 years age group
30
25
20
15
10
5
0
1998
1999
2000
2001
2002
2003
Year

Figure 3. Components of the excess of deaths
Weekly number of death occurrences and components of the excess of deaths, England, 1998 – 2003.

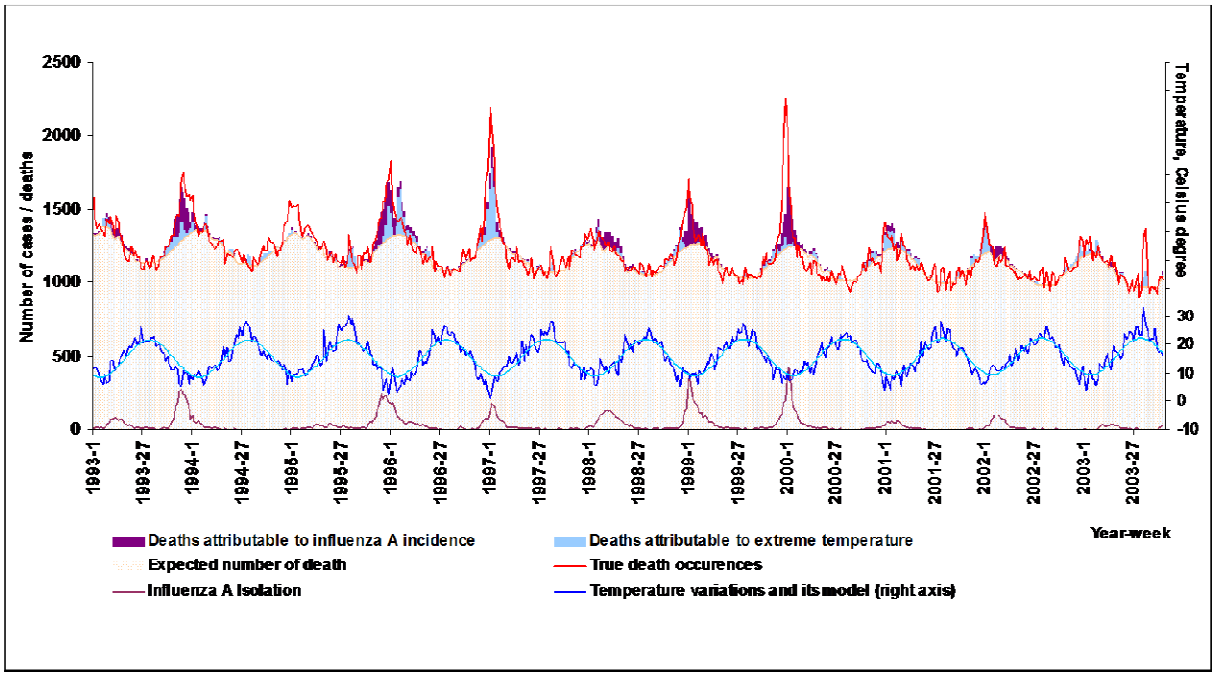
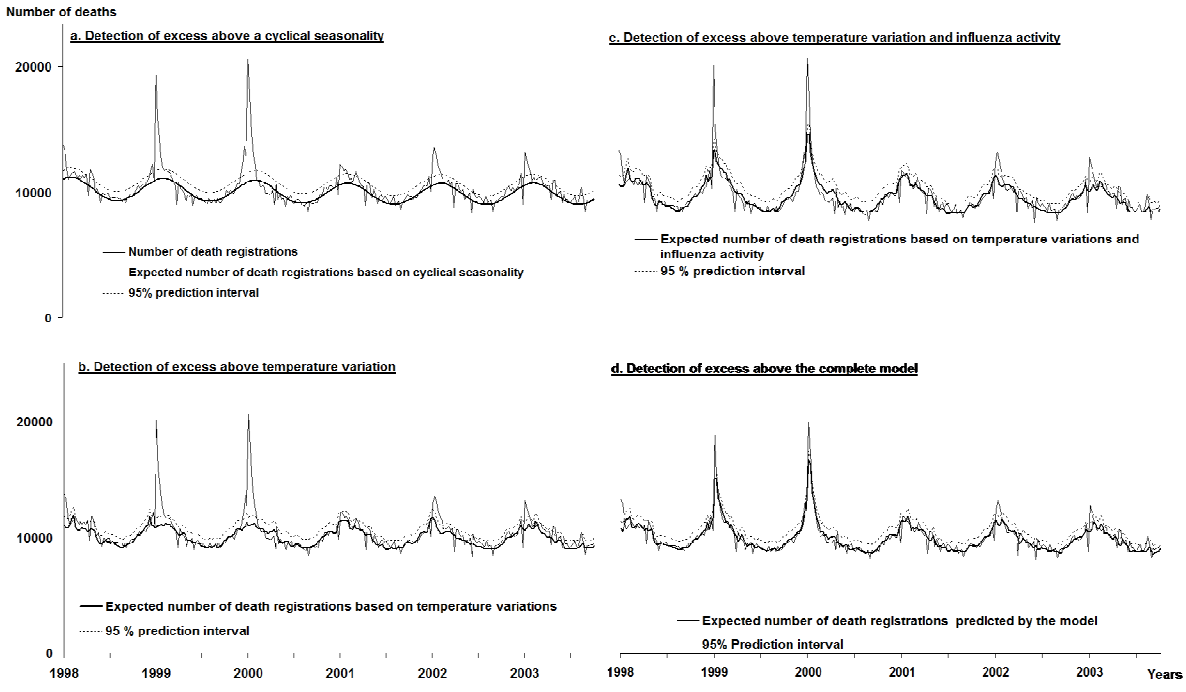


Figure 4: Detection thresholds
Weekly number of death registrations and thresholds for detection of excess, England, 1998-2003



Appendix: Diseases defined for the study, in ICD 9 and ICD 10 codes

Diseases	ICD 9 codes	ICD 10 codes
Cardio-vascular (CA)	390 to 459	I00 to I99
Gastro-intestinal (GA)	520 to 579	K00 to K93
Infectious gastrointestinal (IG)	001 to 009 070	A00 to A09 B15 to B19
Infectious neurological (IN)	320 to 326 036 045 to 049 063 to 064 013 053.0 to 053.1 062 054.3, 055.0, 072.1, 072.2	G00 to G09 A39 A80 to A89 A17.0 to A32.1 B00.3 to B00.4 B01.0 to B01.1 B02.0 to B02.2 B05.0 to B05.1 B22.0, B26.1, B26.2, B37.5, B38.4, B58.2, B94.1, A52.1 to A52.3
Infectious other (IA)	010 to 139 except IN and IG	A15 to B99 except IN and IG
Neurological (NE)	320 to 359	G00 to G99
Renal (RN)	580 to 629	N00 to N99
Respiratory (RE)	460 to 519	J00 to J99

Analysing Finnish mortality data

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Abstract

Introduction

Finland is narrow country, over 1100 kilometres from north to south. The climate is subarctic, although there are significant differences between the extremes. There are no natural barriers such as mountains, so that the climate changes smoothly. The seasons are well defined but vary from year to year and from region to region.

The main issue in analysing mortality data is to estimate the baseline mortality in presence of periods of excess mortality. Such periods occur during catastrophes, heat waves or major epidemics. There seems to be two main approaches. Serfling (1963) proposed analysing the baseline from Spring and Autumn data only, omitting the seasons most likely to have excess periods. Others (such as Farrington 1996) have proposed reanalysing the data omitting large deviations. A priori, the Serflingian method seems less than optimal for the Finnish data, due to the great variations of seasons.

In this paper, we study a third approach by Cantoni and Ronchetti (2001). We conduct a small simulation study to evaluate its performance. We also apply the method on Finnish data with and without covariate adjustments.

Material and methods

Data sources

Mortality data is collected by the Finnish Population Registry (FPR). The official statistics are published by Statistics Finland. For these analyses, the data before 2009 is provided by Statistics Finland in aggregated form. From 2009 onwards the data comes directly from FPR, on individual level, to facilitate the online monitoring.

Weather data comes from Finnish Meteorological Institute. The collection is based on over 400 automatic measuring stations, which are aggregated to subregion levels. There are several variables, but here we use only the mean weekly temperatures.

Influenza data comes from Finnish National Infectious Disease Register (NIDR) and is based on isolations.

Simulations consist of 1000 realizations of 10 years of 52 weeks per configuration. The observations are simulated from a sum of two Poisson variables, baseline and excess. The excess is added to the baseline with probability (contamination rate) varying between seasons. The log-baseline is assumed to have intercept 3 and a single yearly cosine term with amplitude 1. The excess has log-mean 3. Contamination rates are 0, 10, 20, 30, 40 and 50% for the winter, and 0, 5 and 10% for the spring and autumn. Hence there were 6 x 3 x 1000 realizations in total.

Methods

Simulations: The naive analysis is a simple Poisson regression with sine, cosine and linear trend evaluated for full data. The Serfling analysis is same evaluated during active period ISO-weeks 16-25 and 37-44. We use robust regression implemented in R-function `glmrob` (Cantoni 2004) in package `robustbase` (Rousseeuw *et al* 2009), using default options and full data. In Poisson regression the estimation is performed by solving a set of estimating equations. The contribution to this by each observation is called the influence function. For the Poisson regression this is proportional to the Pearson residuals. Robust regression tries to limit the effect of outlying observations by truncating the influence function to a preset value 1.345. The estimating equation is adjusted to achieve consistency (Cantoni and Ronchetti (2001)). For each analysis the baseline is predicted and mean square error (mean of the squared difference between fitted and true baseline), bias (mean difference between fit and true baseline), standard error (mean of the pointwise standard errors of fit over simulations) are reported.

The Finnish data is analysed using the same methods. The trend is modelled as a linear spline with five knots. In addition, the analysis is repeated using seasonally adjusted mean temperature and the interaction between weekly number of influenza isolations and influenza season. For the seasonally adjusted temperature, we model the raw data using sine, cosine and a linear spline trend with five knots. The residuals are then divided into two variables: excess over +2°C and under -2°C. Adjustments are not identified with the Serfling's method so those analyses were omitted. For brevity, only

the results for the whole country are shown. We compare the estimates of baseline and winter/summer excess. In addition, we present the total contribution of each of the elements of the model by influenza year.

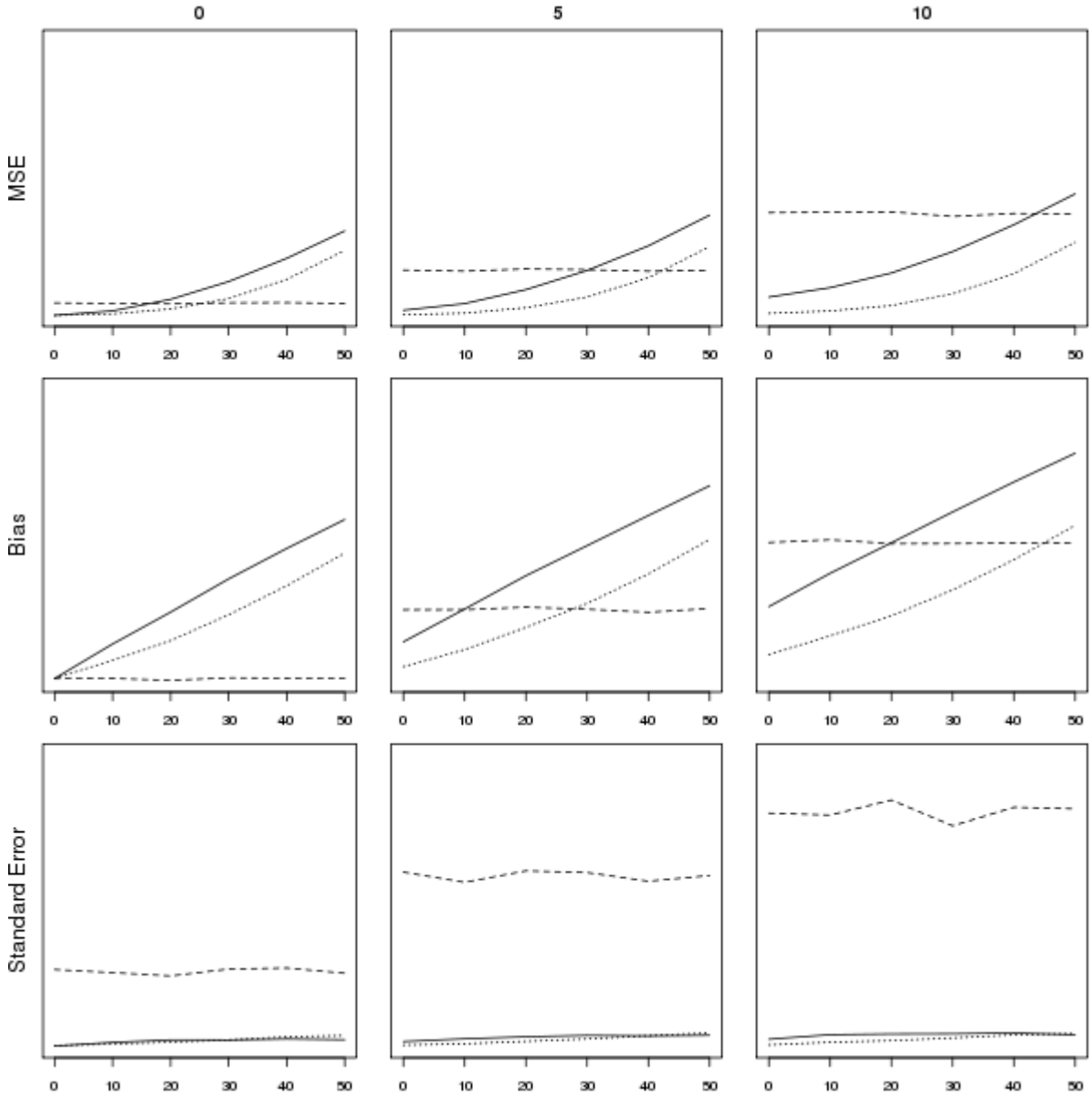
All analyses were done using R version 2.12.2 (R Development Core Team 2011).

Results

The results from the simulations are presented in Figure 1. The Serfling method works rather nicely when there are no excess during the active period. The standard errors are larger than alternatives', which is not surprising, as more than half of the observations are omitted. The robust method is much closer to naive than Serfling results. Robust method seems slightly more tolerant towards contamination during the active period.

Figure 1: Simulation results. Different characteristics for Naive (solid black), Serfling (long dash black), Robust (short dash black) models. X-axis presents the contamination (%) during winter period. Each column has different level of contamination during the

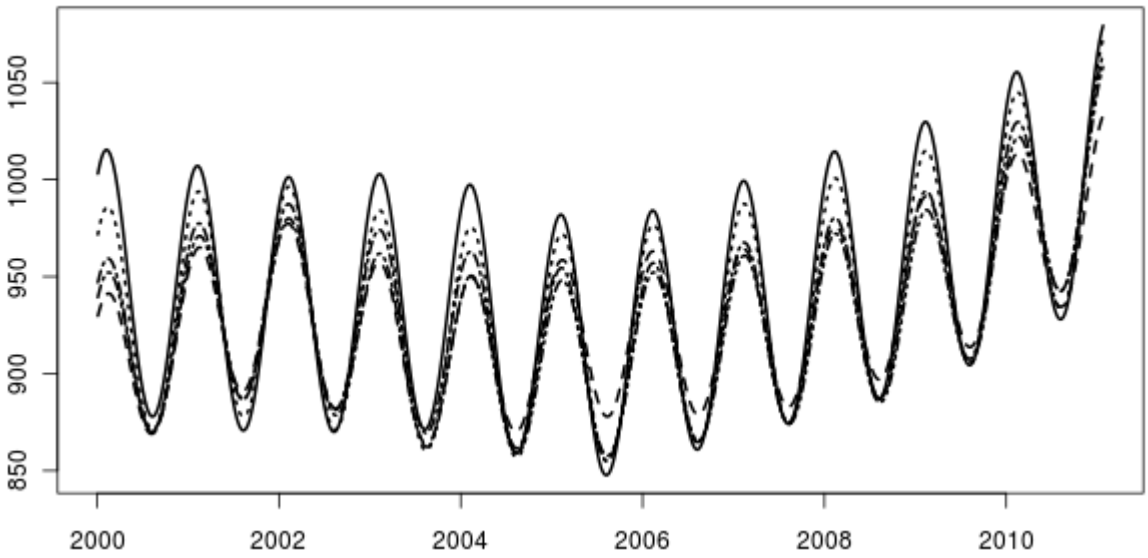
active period.



The estimated baseline for the Finnish data results are in Figure 2. As expected, Serfling estimates are lower and have smaller amplitude than other estimates. Robust method offers surprisingly little adjustment over naive model. Adjustment brings both naive and robust methods closer to Serfling.

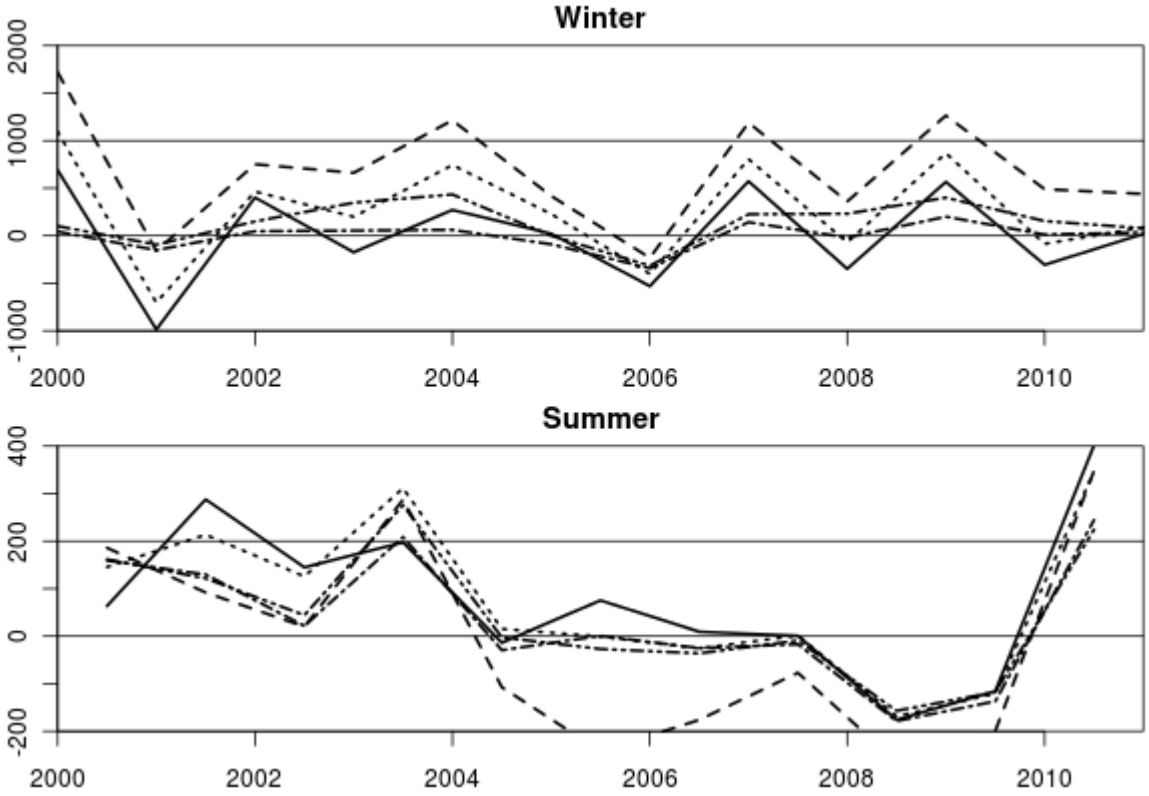
Figure 2: Baseline estimates from different models for the Finnish data: Naive (solid), Serfling (long dash), Robust (short dash black), Adjusted (long dash short dash), Robust adjusted (long dash two

short dashes).



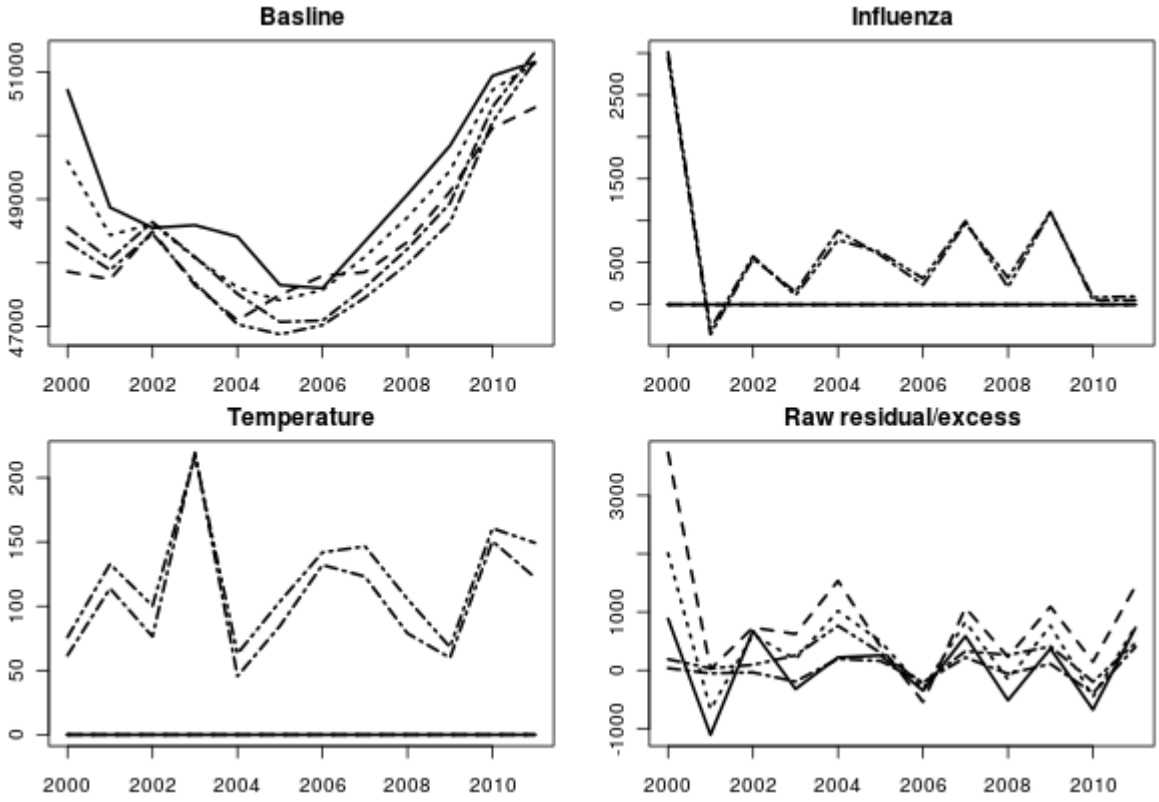
Excess estimates for winter and summer (Figure 3) are higher using the Serfling's method, whereas robust method lies somewhere between. Adjustments seem to work better during the winter season, due to the larger number of cases.

Figure 3: Estimated number of excess cases by season and year: Naive (solid), Serfling (long dash), Robust (short dash black), Adjusted (long dash short dash), Robust adjusted (long dash two short dashes).



The contribution of the baseline follows naturally the estimates of the trend (Figure 4). The effect of the weather seems relatively constant, whereas that of influenza varies greatly. The adjustments do not remove all year to year variation, suggesting need for either more detailed modelling or additional covariates.

Figure 4: Estimated contributions to the total mortality: Naive (solid), Serfling (long dash), Robust (short dash black), Adjusted (long dash short dash), Robust adjusted (long dash two short dashes).



Conclusions

There is a distinct need for handling contamination (excess) in mortality data. Serfling's method is widely used and proven robust. This is partially confirmed in our simulation results. However, the simulation model is overly simple and especially well suited for Serfling method. For instance, it does not have any seasonal variations typical to the Finnish data. Even in this optimal case, the Serfling's method has larger standard errors. If the active period is estimated from, say, historical data or external covariates like weather, the uncertainty in this estimation should increase the standard errors even further.

Robust methods provide good theoretical framework for assessing the excess. It is readily available in R. As expected, it's performance seems to be a compromise between the other methods, albeit being

slightly closer to the naive method. Unlike Serfling's, it allows for covariate adjustments.

Our application of the robust method does not utilize all of its potential: The influence function is symmetric, even though additivity of the excesses would suggest asymmetrical. We did not try to estimate optimal threshold. We did not evaluate other similar Robust methods available in R.

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3. The added European value

Pooling data from several member states to maximise the European value (Jens Nielsen)

Introduction

The general objective of EuroMOMO is to develop and operate a routine public-health mortality-monitoring system for detecting and measuring, in a timely manner, excess number of deaths related to public-health threats across Europe. The backbone of EuroMOMO is country-specific or regional monitoring of number of deaths, and these national data are analysed by member states using the A-MOMO package developed in WP7. This model may reveal changes in number of deaths at the national level. However, small but sustained changes in number of deaths may not give rise to significant signals in the local monitoring. However, combining data across countries may decrease the variation around the baseline and thus increase the signal-to-noise ratio. Hence, small changes in excess mortality may be noticeable in an analysis including data from several member states, in particular if the changes occur simultaneously. Likewise, combining across countries can also be useful for monitoring of changes in mortality in smaller groups with an expected low number of deaths, e.g., younger age groups or fertile women. Except for very dramatic events, local monitoring of such populations will lack statistical power. Finally, analyses at member state level may not reveal patterns across Europe such as movement of diseases between countries. Hence, there is a need for combining and analysing data across the European countries.

Number of deaths from countries with varying numbers of inhabitants will not be compatible; neither will crude excess number of deaths. However, a standard score (z-score) that indicates how many standard deviations the observed weekly number of deaths is above or below the baseline is comparable between countries and over time (as described in the A-MOMO Guidebook of WP7). Differences in pattern in number of excess deaths between countries can be analysed by comparing the z-scores from different countries. In the present chapter, we add to the national outputs a z-score based on *combined data* from a number of different member states. This approach may reveal European patterns that are unnoticed by member states and provides an outcome describing national and European patterns of excess mortality and changes in number of deaths.

We present and discuss methods for combining data and conducting pooled analyses, and apply data from the weekly reporting to EuroMOMO from participating countries to investigate differences between age groups and effect of the influenza A H1N1 pandemic in 2009/10.

Methods

Data

Fifteen countries participated in the pilot study collecting local data on number of deaths (WP8), process these locally by the A-MOMO program package (for details see A-MOMO Guidebook), and send output from A-MOMO to the EuroMOMO

project hub at Statens Serum Institut (SSI), Denmark, on a weekly basis. Data received from each country by the hub were aggregated by week (total), and by week and age group (0-4, 5-14, 15-64 and 65 years of age or above), and contained information on number of deaths registered and number of deaths corrected for delay in reporting. Data also contained weekly information on expected number of deaths (baseline) and excess number of deaths (delay adjusted deaths - baseline) as well as a z-score expressing the relative derivation from the baseline (see Appendix, Formulas). Weekly input from submitting countries was combined and used as data for pooled analyses. Only weeks where data from all countries included were available simultaneously was used for pooled analyses.

3.1 Pooling data: Methodological considerations

When pooling data the following has to be considered:

- Adjustment for delay in reporting.
  Different countries have different delays in their reporting of deaths, and no overall delay is available. Using locally delay adjusted number of deaths from each country would create a locally delay-adjusted number of deaths and thus overcome the challenge of different delays between countries.
- Calendar period included in the pooled analyses.
  Pooled analyses are only feasible for weeks where data from all countries is available simultaneously. Hence, the pooled data included in the estimation of the historical baseline will be limited to the period where all countries were able to provide data. This may cause a discrepancy between local and pooled analyses, as they will not be based on the same historical calendar interval in all countries.
- Heterogeneity between countries
  Countries may have different patterns of mortality, e.g. larger impact of winter excess mortality in Northern countries and heat wave excess mortality in the Mediterranean countries. Variation in mortality may also be different. Hence, mortality patterns may not be homogeneous in pattern and variation across countries

A straightforward approach to pool data would be to regard participating member states as one “country” (Europe) by summarising the weekly number of delay-adjusted deaths from the different member states (solving the first point). These summarised data may then be analysed as representing one overall country, using the same procedures as for each separate country by applying the A-MOMO package. This approach is called the summarised method. However, this method has some shortcomings. The second point with a potential discrepancy between the local and the pooled historical baseline cannot be circumvented using the summarised method. Neither can the third point, because the summarised method implies regarding all countries as one overall homogeneous country both concerning mortality pattern and variation.

Another method accounting for differences between countries, like duration and peaks in influenza associated deaths, and differences in calendar intervals would be to use the local baselines directly in country-stratified pooled analyses. This approach is called the stratified method. It can be carried out by summarising both local weekly number of delay adjusted deaths and expected number of deaths. An advantage of the

stratified method is that the pooled baseline will not be restricted to one sine curve, but will be a combined curve of the local sine curves. Hence, the stratified method provides not only locally delay-adjusted numbers of deaths and excess, but is also adjusted to differences in mortality pattern. Further, assuming (statistical) independence between the countries, the variance of the summarised weekly excesses can be calculated directly from the estimated variances of the national excesses (see Appendix), thereby, also adjusting for heterogeneity in variation. The shortcoming of this method will be the assumed independence between countries.

The two methods, summarised and stratified, will be compared, and the preferred used to combine data for pooled analyses.

3.2. Age pattern in number of deaths

Seasonal pattern in infectious diseases and environmental conditions like temperature causes seasonal pattern in illness and deaths, especially in vulnerable groups like for example children and elderly.
Age pattern in number and excess number of deaths across Europe were explored using pooled analyses and data from EuroMOMO based on the national estimates of the weekly number of deaths in the age groups 0-4, 5-14, 15-64 and 65 years of age or above.

3.3. Effect of the 2009/10 influenza A H1N1 pandemic

A specific objective of the EuroMOMO project was to obtain rapid estimates of any effect the 2009 influenza A H1N1 pandemic had on overall mortality [Mazick et al. 2010]. In the EuroMOMO routine output, the effect on mortality was expressed as the weekly excess number of deaths over the calendar period the population(s) was exposed to the pandemic. This measure reflects the time-pattern of the impact of the pandemic, but not the total number of excess deaths over time. However, the cumulated number of excess deaths over calendar time through the pandemic period provides an estimate of the running overall effect through the period. This measure includes any changes that occurred due to time-shift in usual mortality and the so called harvest effects, i.e., premature death of individuals with severe underlying illness that were bound to die anyway. Cumulated number of excess deaths depends on the number of inhabitants and does not reveal if the excesses are minor or major. The cumulated excess relative to the cumulated expected number of deaths will quantify the magnitude of the excess without the need to calculate specific excess mortality rates.

Every year has a winter period with increased mortality due to influenza and other seasonal infections; extreme (cold) temperatures may also have an impact. As it is the aim of EuroMOMO to measure this excess mortality, in most seasons the algorithm is designed to estimate the expected number of deaths (baseline) below winter excess. Therefore, the cumulative excess for the pandemic period was also compared to the cumulative excesses the previous seasons to see if the pandemic excess was different from the previous seasons in size and/or pattern.

The H1N1 pandemic season was defined as 1 year from week 27, 2009 to week 26, 2010. The pooled effect of the H1N1 pandemic was investigated as the relative (%)

cumulated excess compared to the cumulated expected number of deaths over the period of the pandemic. This was done for the total pooled data, and for each pooled age group to reveal differences in the effect of the pandemic between different age groups.

Results

Data

Data from 13 countries (Belgium, Denmark, Finland, France, Greece (Counties: Athens, Kerkira, Keratsini, Magnesia, Kavala), Hessen (in Germany), Ireland, Israel, Netherlands, Portugal, Spain, Sweden and Switzerland), locally processed by the A-MOMO package was used. Information from all of these countries was available simultaneously from week 25, 2007 to and including week 36, 2010.

Method for pooling data

The baseline (expected number of deaths) based on the historical period from week 25, 2007 to week 36, 2010 estimated using the summarised method was different from the baseline based on the local historical periods in the stratified method (Figure 1, left panel), both in trend and seasonal amplitude.
The summarised method suppresses heterogeneity in variation between countries i.e. gives a lower pooled variance implying increased z-scores (Figure 1, right panel), and may as thus over-emphasize the pooled effect to out of the range of the county specific z-scores e.g. in the season 2008/9.
Therefore, the stratified method was preferred, as it account for heterogeneities in both pattern and variation across countries.

Pooled analyses

The stratified method was used to calculate the across all countries pooled delay-adjusted number and expected number of deaths for all ages (Figure 2, top panel) and age groups (Figure 3). Between countries comparable z-scores together with country specific z-scores for all ages are shown in figure 2 (bottom panel) and for age groups in figure 4.

The pooled z-score do not express a “mean” z-score i.e. stay more-or-less in the middle of the country wise z-scores (Figure 2, bottom panel). The pooled z-score follow and emphasizes coinciding tendencies in the country specific z-scores, for example during the heat-wave in July 2010.

The winter seasons 2007/8 and 2008/9 had peaks in excess number of deaths surpassing 4 z-scores, and it was mainly among persons aged 65. In the season 2009/10 the peak was not that pronounced, but spread over a longer period. We observed an early peak in November 2009 (around week 44) mainly in the age group 5-14 years of age. A second peak in December/January, mainly among persons aged 65 and corresponding to the peaks in the previous season, though less pronounced, and a late third peak in February 2010 among elderly.

Age pattern in mortality

Generally, there was a declining trend over calendar time in number of deaths for persons below 65 year of age, and a stable number of deaths for those aged 65 (Figure 3). There was no recognisable seasonal pattern in number of deaths among children, but as age increased a seasonal pattern became more and more prominent. With increasing age a pattern of increasing excess number of deaths in the winter season emerges. This pattern was also seen in the country wise analyses (data not shown).

Comparing excess deaths across countries by z-scores (figure 4) show an increasing relative fluctuation with age, and as also seen for the nominal numbers winter-season excesses increases with age.

Effect of the H1N1 pandemic

The percentage of pooled cumulated excess number of deaths relative to the expected number of deaths during the H1N1 pandemic season 2009/2010 is shown in figure 5.
For children below 5 year of age the excess number of deaths grew through autumn of 2009 to around 5%; 4.8% (-0.1%-14.3%) in the last week of 2009. Then it slowly declined to around 3%; 2.9% (-0.6%-10.6%) in week 26, 2010.
Among children 5 to 14 years of age there was a slight peak late summer/early autumn (27.8% (0.1%-77.4%) in week 33, 2009) that was compensated through autumn. By the end of autumn and to the end of the year it increased again; peak: 18.0% (-0.4%-53.9%) in week 49, 2009. From the beginning of 2010 it slowly declined to around a 6% excess number of deaths: 6.3% (-5.2%-30.8%) in week 26, 2010.
Relative excess number of deaths in the age group 15 to 64 years of age was not increased until by the end of autumn 2009, when it start to increase until March 2010; statistically significant from week 49, 2009 and peaking with 2.1% (0.9%-3.6%) in week 11, 2010. From March and onward it decreased to 1.2% (0.3%-2.5%) in week 26, 2010.
For those aged 65 started the season 2009/2010 with an increased relative number of deaths probably due to repercussions of the summer heat waves. There was no marked excess number of deaths through autumn, but from end of 2009 and until March there was a significant increase in relative number of deaths peaking in week 11, 2010; 3.0% (2.1%-4.1%). Then it declined to just below 3%; 2.7% (1.8%-3.7%) in week 26, 2010.
As the major part of deaths is among the elderly and none of the younger age groups had very high nominal excesses the total excess over all age groups followed the pattern of the elderly.

Children below 5 years of age had an earlier increased excess number of deaths in the H1N1 pandemic season compared to the two previous seasons (Figure 6). Starting to increase already from week 35 and being above the previous season until end of January the following year, ending up with the same relative number of excess deaths as in the previous seasons. The same pattern is seen for children 5 to 14 years of age, where H1N1 was above the previous seasons from around week 43 to April the following year.
For adults, 15 to 64 years of age, there were no differences in pattern of excess between the H1N1 season and the previous two seasons. For those aged 65 the relative H1N1 excess was the same as or below the previous seasons.

Discussion

Pooled analyses over countries of number of deaths are an important part of routine public-health mortality surveillance across Europe, both because it may reveal changes that may have passed unnoticed in the country specific surveillance, due to more statistical power, and because it will give a picture of the general development in mortality across Europe.

Two methods were investigated and the stratified method is recommended as it accounts for heterogeneity between countries in both pattern and variation. The shortcoming of the stratified method is the assumed independence between countries. Illnesses spread from country to country, why the correlation between bordering countries probably will be positive i.e. changing in the same direction. Positive correlation will increase the variance, which again will imply lower z-scores. On the other hand, if an illness moves across countries then deaths might be decreasing in the "hosting" country, and increasing in the "receiving" country i.e. negative correlation. However, there was no indication of this in our data. Illnesses spread too quickly over Europe to see either a positive or negative correlation on the delayed effect of illnesses on mortality. If anything the correlation will probably be mainly positive, and the assumption about independence implies that the pooled z-scores may be slightly overestimated.
The z-scores calculated using the stratified method stayed within the range of the country specific z-scores (Figure 2 and 4) and may therefore be accepted and used as a reliable indicator of overall changes in mortality over the countries. However it should always be interpreted together with the country specific z-scores, because country specific peaks may vanish in the pooled analyses.

The time series of numbers of deaths and z-scores (Figure 2, 3 and 4) shows that the winter season 2007/8 had a peak in December/January likely to be a combination of influenza A H3N2 and excess Christmas mortality, while the elevated number of deaths through spring was likely to have been associated to influenza B. The high peak in early 2009 coincides with the 2008/9 influenza season, which was more intense than the previous season and dominated by influenza A H3N2. In the winter seasons 2007/8 and 2008/9 it was primarily elderly that were affected. In contrast, only modest excess mortality was seen in the winter season 2009/10 with the pandemic influenza A H1N1. However, there was a small peak around week 48, 2009 among 5 to 14 year old children, and a December/January peak among the elderly. In February 2010 a peak likely to be associated to the cold snap was observed. Further, increased mortality primarily among elderly were observed in the summers of 2008 and 2010; both coinciding with heat waves experienced in many European countries.

Estimated baselines showed a declining trend over calendar time in number of deaths for persons below 65 year of age, and a stable number of deaths for those aged 65 (Figure 3). This is probably due to the generally aging populations in Europe i.e. number of young habitants decline. With the same mortality this will imply that number of deaths will be declining in the younger age groups.
The z-scores for children mainly were stable over calendar time (Figure 4) i.e. unaffected by season and other environmental extremes like heat waves or cold snaps. For adults and elderly a more and more significant seasonal pattern emerges with age,

probably due to an increasing vulnerability to influenza and other seasonal illnesses with age.

The 2009/10 pandemic influenza A H1N1 had virtually no effect on mortality, especially compared to the two preceding seasons. An early increased excess in number of deaths was observed among children 5 to 14 years of age, as also had been reported earlier in a pooled analyses with eight countries [Mazick et al. 2010]. However, compared to the preceding seasons it disappeared again, thus ending the season at the same level as the preceding seasons, likely due to harvest effects. This is probably because the H1N1 pandemic influenza A virus shares similarities with H1N1 viruses circulating before the 1957 pandemic [WHO 2010]. Hence, persons in the mid-50s and above had some cross-immunity and were relatively spared [Donaldson et al 2009, Nicoll and McKee 2010]. Children had no immunisation from earlier and vaccinations in many countries first became available at the peak of the influenza or just after. Hence, vulnerable children were unprotected in the start and this was why excess numbers of deaths was observed early in the season. The early unprotected period had probably mainly affected the most vulnerable children; those that probably would have died anyway. Hence, the total excess number of deaths among children over the whole season ended up being the same as for the preceding seasons.

3.4 Conclusion and recommendation

A few countries have chosen in the weekly reporting to provide a limited dataset i.e. a dataset without observed and expected numbers of deaths, but only relative derivation from the baseline (z-scores), for the weekly surveillance of mortality. Data from these countries cannot be included in the routine weekly pooled analyses. However, these countries could be included in the pooled analyses, if they provided complete data to the EuroMOMO hub, and the hub take responsibility for only publishing country specific z-scores for countries now providing limited data.
For the pooled analyses to be a useful tool in public heath surveillance it is important that as many countries as possible participate, and they participate every week.

Pooled analyses is influenced mostly by countries with most inhabitants i.e. having the largest number of deaths, which implies that extreme excess in smaller countries may be un-noticed or in large countries indicate an excess number of deaths all over Europe, though it is only local. Hence, it is important that the pooled analyses are interpreted in combination with country specific analyses. Therefore we recommend the pooled analysis shown in figure 2, where the polled z-score are supplemented with the country specific z-scores.

Pooled analyses can reveal changes in number of deaths that would have been unnoticed in the separate country analyses. Hence, timely pooled analyses can be a valuable tool in public health surveillance, especially for smaller or vulnerable groups like infants and young children or women in the fertile age.

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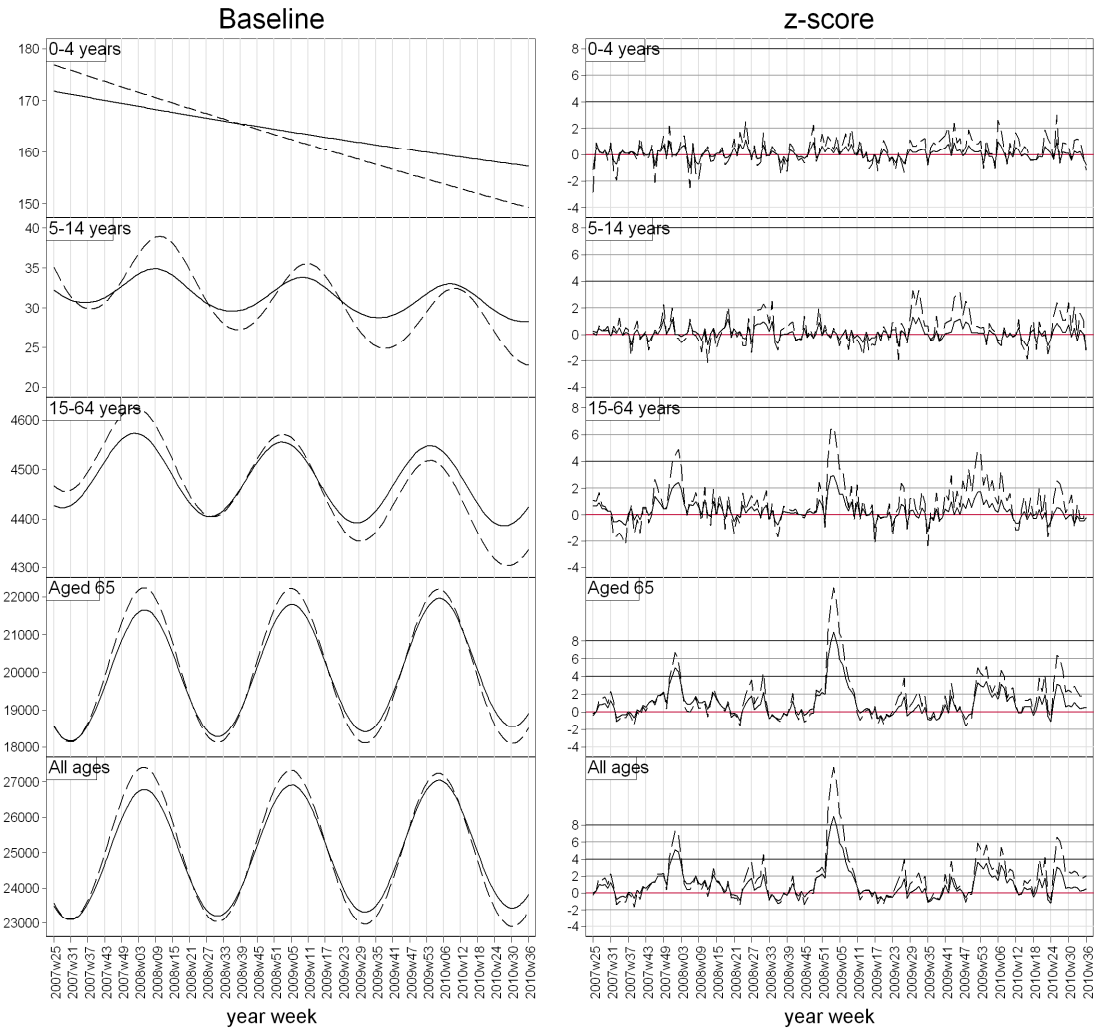
Figure 1. Comparing the two methods: summarised and stratified



Full line: Stratified. Dotted: Summarised

Figure 2. Pooled analyses for all ages using the stratified method

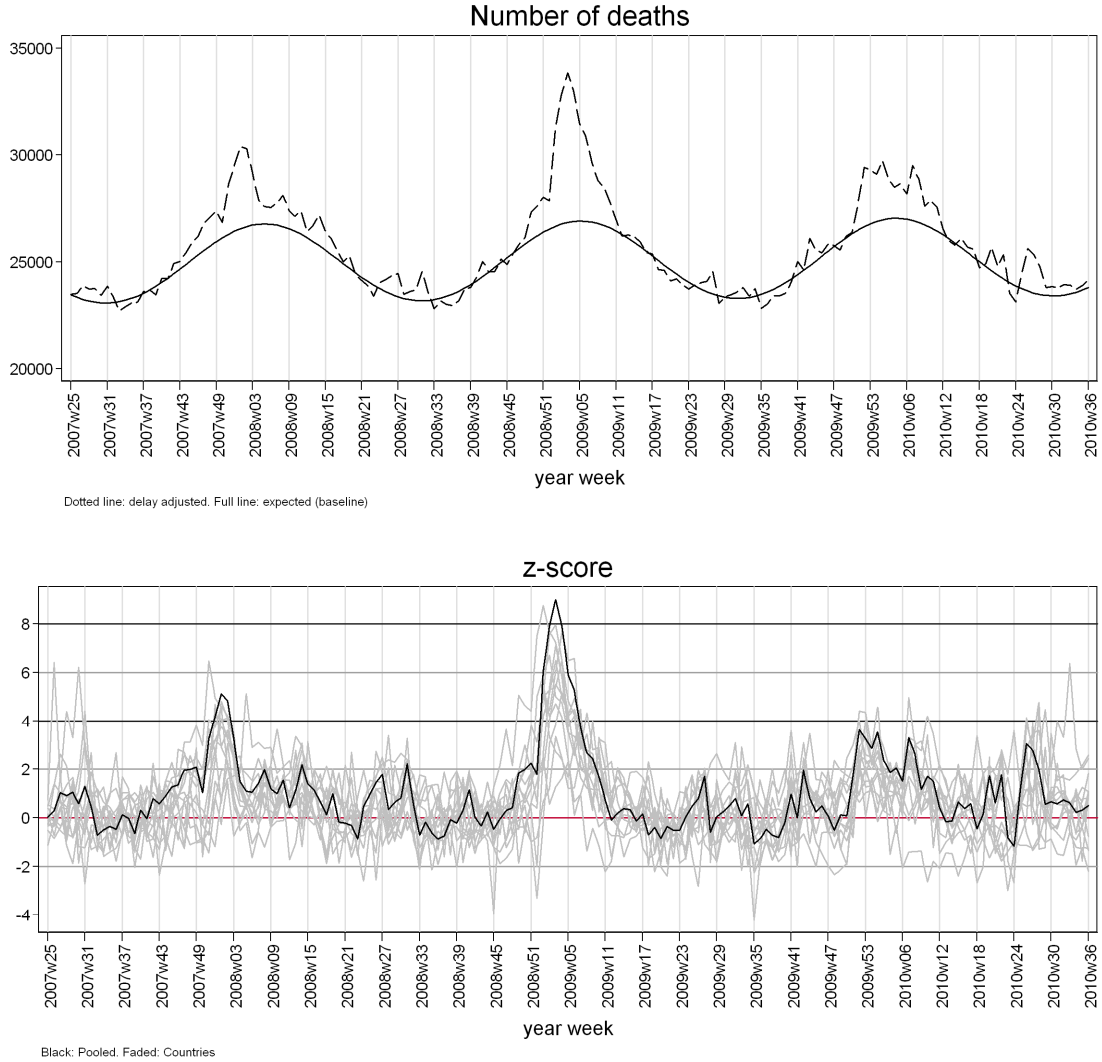


Figure 3. Pooled delay-adjusted and expected number of deaths by age group

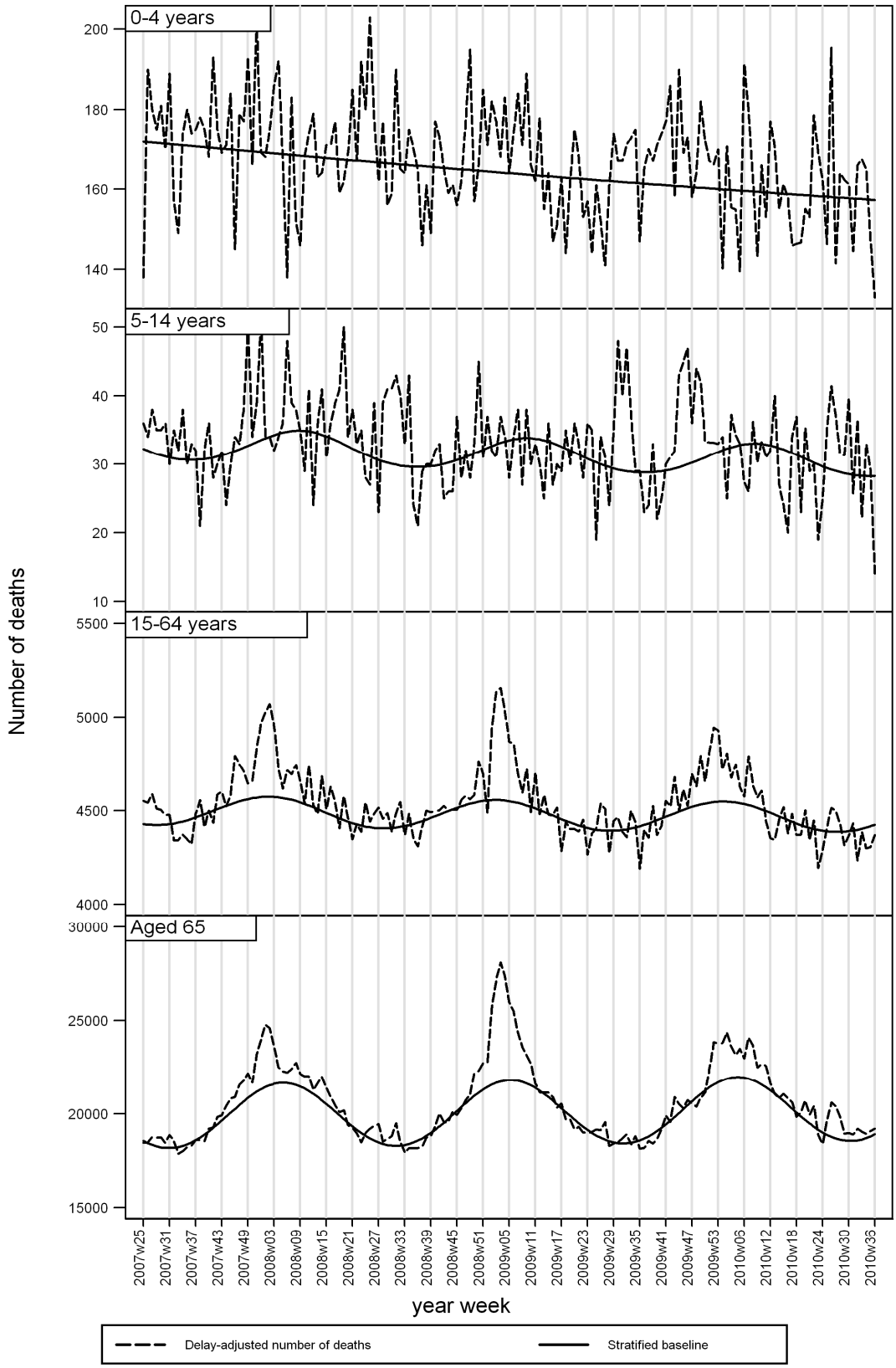


Figure 4. Pooled and country z-scores by age group

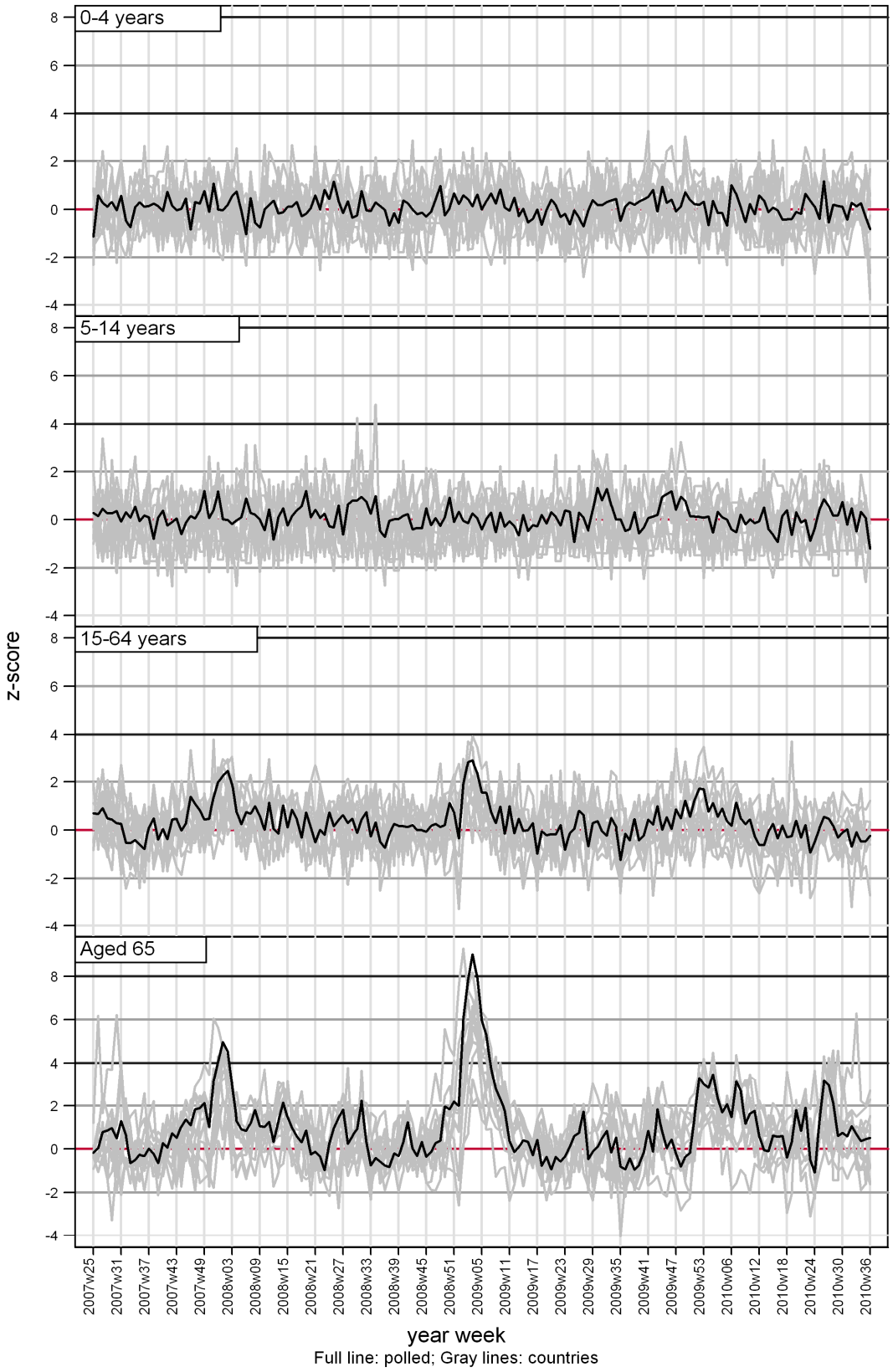


Figure 5. The influenza A H1N1 pandemic. Pooled relative cumulated excess number of deaths by age group and total

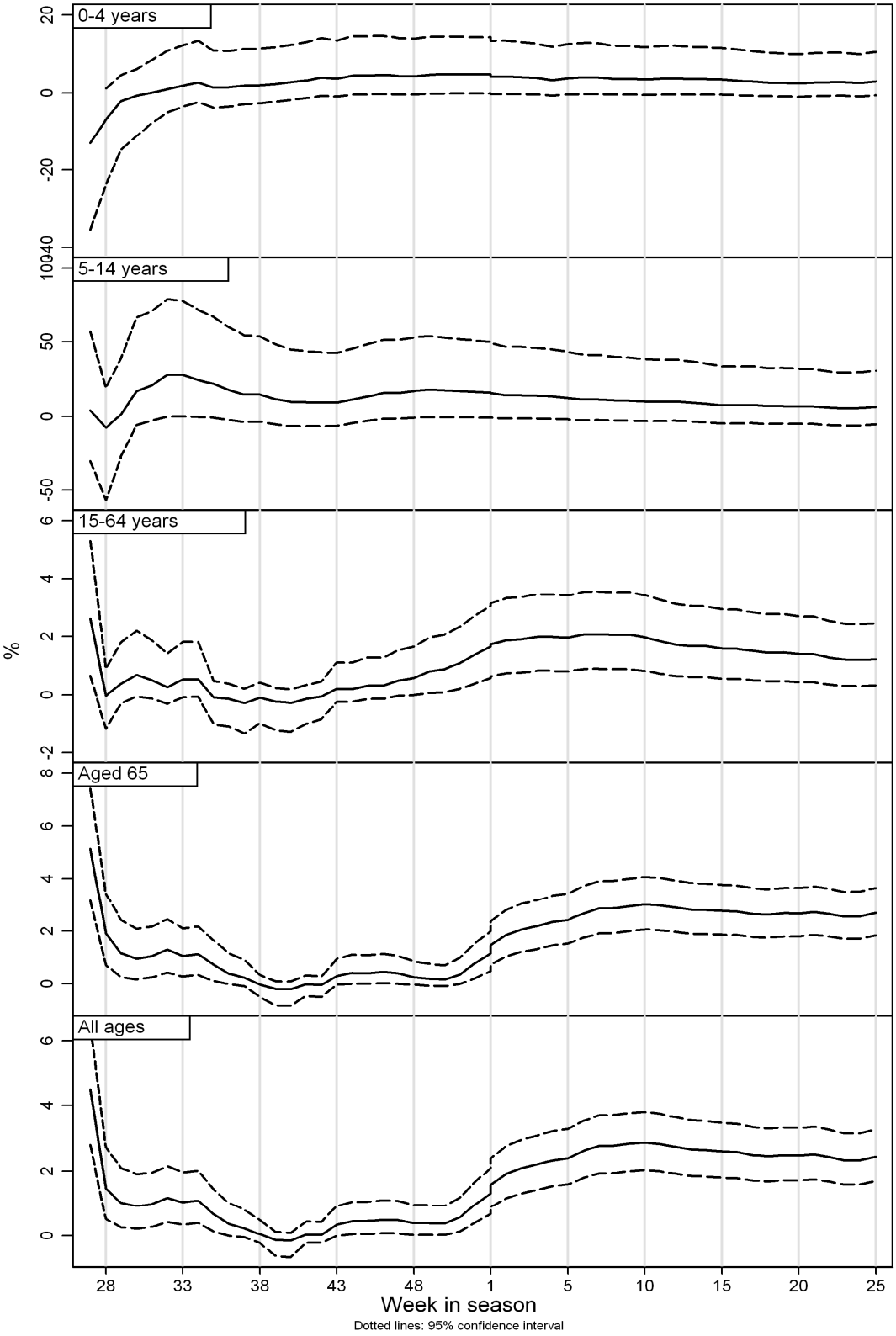
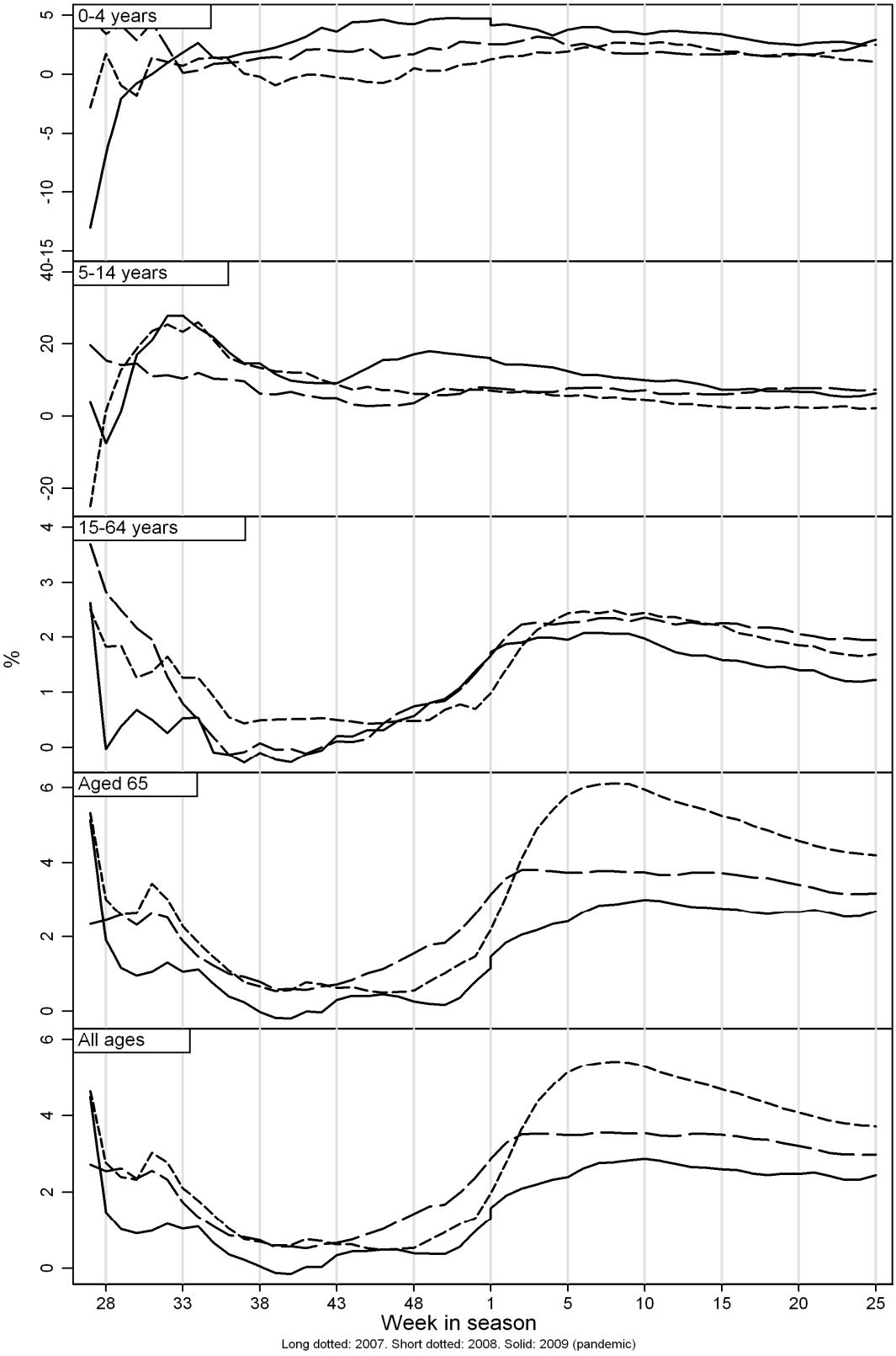


Figure 6. Polled relative excess number of deaths in the influenza A H1N1 pandemic season and previous seasons.



APPENDIX: Formulas

Variance and z-score in the A-MOMO package

In the A-MOMO package weekly z-scores was calculated in a ⅔ power transformation to correct for skewness [Farrington et al. 1996]. Generally, for any power transformation:

$$\text{z-score} = (nbc^{\gamma} - pnb^{\gamma}) / \sqrt{\text{Var}(nbc^{\gamma} - pnb^{\gamma})}$$

where pnb is the predicted number of deaths (baseline), nbc is number of deaths corrected for delay in reporting, and γ is the power transformation e.g. ⅔.
An approximation to the variance of $(nbc^{\gamma} - pnb^{\gamma})$ was calculated using the delta method [Farrington et al. 1996, Cox 2005]: $\text{Var}(f(X)) \approx (f'(E(X))^2 \cdot \text{Var}(X)$:

$$\begin{aligned}\text{Var}(nbc^{\gamma} - pnb^{\gamma}) &= \text{Var}(nbc^{\gamma}) + \text{Var}(pnb^{\gamma}) \\ &\approx (\gamma\, E(nbc)^{\gamma-1})^2\, \text{Var}(nbc) + \text{Var}(pnb^{\gamma})\end{aligned}$$

where $\text{Var}(pnb^{\gamma})$ is the variance (standard error squared) of the predicted/expected number of deaths estimated by the model, which was a Poisson regression with overdispersion i.e. $\text{Var}(pnb^{\gamma})$ is a known outcome from the regression. The observed numbers of deaths (nbc) will, as they come from a Poisson distribution with overdispersion φ, have the variance $\text{Var}(nbc) = \varphi \cdot nbc$. Further, weekly data was aggregated, why $E(nbc) = nbc$. Hence,

$$\text{Var}(nbc^{\gamma} - pnb^{\gamma}) \approx (\gamma\, nbc^{\gamma-1})^2\, \varphi\, nbc + \text{Var}(pnb^{\gamma})$$

and the z-score was approximately calculated as:

$$\text{z-score} \approx (nbc^{\gamma} - pnb^{\gamma}) / \sqrt{(\gamma\, nbc^{\gamma-1})^2\, \varphi\, nbc + \text{Var}(pnb^{\gamma})}$$

Variance and z-score in the pooled analyses

In the stratified method and assuming (statistical) independence, local power transformed variances of excess was added to provide a pooled power transformed variance of the pooled excess number of deaths. Thus, correcting for skewness in the pooled data.
The local power transformed variances of excess was not included in the A-MOMO output received from the countries, but can be calculated by inverting the formula for the local z-score, as this as well as pnb and nbc are known:

$$\text{Var}_{\text{local}}(nbc^{\gamma} - pnb^{\gamma}) = ((nbc^{\gamma} - pnb^{\gamma}) / \text{z-score})^2$$

The pooled variance of the power transformed excess = $((\sum nbc)^{\gamma} - (\sum pnb)^{\gamma})$ then become:

$$\begin{aligned}\text{Var}((\sum nbc)^{\gamma} - (\sum pnb)^{\gamma}) &= \sum \text{Var}_{\text{local}}(nbc^{\gamma} - pnb^{\gamma}) \\ &= \sum ((nbc^{\gamma} - pnb^{\gamma}) / \text{z-score})^2\end{aligned}$$

and the pooled z-score become:

$$\text{z-score} = ((\sum nbc)^{\gamma} - (\sum pnb)^{\gamma}) / \sqrt{\text{Var}((\sum nbc)^{\gamma} - (\sum pnb)^{\gamma})}$$
$$= ((\sum nbc)^{\gamma} - (\sum pnb)^{\gamma}) / \sqrt{\sum ((nbc^{\gamma} - pnb^{\gamma}) / \text{z-score})^2}$$

Confidence intervals for the pooled weekly excess = ($\sum$nbc - $\sum$pnb) can be calculated by:

$$95\%CI(\text{excess}) = [(\text{excess})^{\gamma} \pm 1.96 \sqrt{\text{Var}((\sum nbc)^{\gamma} - (\sum pnb)^{\gamma})}\ ]^{1/\gamma}$$
$$= [(\sum nbc - \sum pnb)^{\gamma} \pm 1.96 \sqrt{\sum ((nbc^{\gamma} - pnb^{\gamma}) / \text{z-score})^2}\ ]^{1/\gamma}$$

For the cumulated excess, used to investigate effect of the H1N1 pandemic, the confidence interval was calculated as:

$$[\ (\sum^{W}(\sum nbc - \sum pnb))^{\gamma} \pm 1.96 \sqrt{\sum^{W} \sum ((nbc^{\gamma} - pnb^{\gamma}) / \text{z-score})^2}\ ]^{1/\gamma}$$

Where $\sum$ is sum over countries and $\sum^{W}$ is summing from week 1 to week W.

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