THE IMPACT OF INFLUENZA

an epidemiological study of morbidity, direct mortality & related mortality

De Gevolgen van Influenza,
een epidemiologische studie naar ziekte,
direkte sterfte & gerelateerde sterfte

Proefschrift

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If you accept the challenge, you are obliged to it

aan mijn overleden grootvader,
aan mijn ouders,
aan Myriam, Brigitte en ...

Contents

Introduction

In 1918 and 1919, the largest part of the world was affected by a devastating epidemic of influenza. Comparatively at the close of the First World War, influenza was responsible for more deaths than four years of fighting.[1] Striking was the fact that mortality was highest in the age group that should be most resistant to disease. Young, vigorous adults, those between the ages of twenty and forty, were most susceptible to the ravages of the epidemic[2].

The purpose of this dissertation is to assess the impact of influenza in The Netherlands during an extensive observation period of 22.5 years. This observation period includes the well-known Hong-Kong epidemics (from 1968) as well as other (unknown) minor epidemics until 1989. It is tried to determine as precise as possible the subpopulation who is at highest risk to die due to influenza or in association with influenza. Since a preventive vaccine is at disposal it is very important to delineate that subpopulation so that the vaccine can be used especially in that group.

In the first chapter the influence of influenza on the mortality from heart and lung diseases is assessed, in people over 70 years of age, on the basis of data received from the Dutch Central Bureau of Statistics. The observed monthly mortality data concerning heart and lung diseases (influenza not included) are used to fit a regression model.
The model includes three explanatory variables: calendar year and month and the overall monthly number of influenza mortality cases, assuming that monthly mortality is generated by a Poisson process. The monthly excess mortality from heart and lung diseases due to influenza among elderly people (> 70 years) is estimated on the basis of the fitted regression equation.

In the second chapter the total impact of influenza is similarly estimated, considering the total population (all ages) and total mortality (all death causes except influenza). In order to delineate which people are at risk, death causes are divided into three groups. For practical reasons the death causes will be divided into: 1. heart disease, 2. lung disease and 3. other death causes.

In the further analysis the heart diseases will again be subdivided into five death causes and lung diseases into two death causes. Four age groups will be considered: 0-59 years, 60-69 years, 70-79 years and 80 years and over.

In chapter three the relationship is investigated between the number of influenza-like illnesses (ILI), weekly registered by the general practitioners (sentinel-stations), and the monthly overall influenza-mortality, given by the Dutch Central Bureau of Statistics during the period July 1970 to June 1989.

The quantitative impact of influenza-morbidity is expressed by three summary parameters, deduced from the weekly ILI-figures, (i.) their sum (i.e. global extent of an epidemic), (ii.) their standard deviation, and (iii.) their maximum (i.e. peak number of ILI during an epidemic). These three parameters are mutually compared with respect to their predictability for total influenza mortality in the 19 season-years available.
No distinction is made between Influenza A and B or any subtype of influenza A, because no reliable figures of the incidence of each subtype are available.

In chapter four a recent occurrence of excess mortality is discussed.

In the final chapter (5) the general conclusions are presented with recommendations for the influenza surveillance and prevention.

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Influenza mortality and excess deaths in the elderly, 1967-1982

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Introduction

For many diseases mortality is an essential measure of incidence in epidemiologic studies and its long-term trends form the basis for vital statistics. This is also valid for influenza. In 1848 Farr[1] described this in detail for the epidemics in London in 1847. He introduced the concept of excess mortality, defining it as the number of deaths over and above the expected number for the particular season in which, and the place where, the epidemic occurred. The use of mortality statistics has been the most widely used tool for characterization of influenza epidemics on a worldwide basis since the pandemic of 1889-91[2]. Both Frost[3] and Collins[4] applied Farr's concept of excess mortality to influenza and Housworth and Langmuir[5] showed that there was excess mortality from heart, circulatory and nervous disorders during influenza epidemics and outbreaks occurring between 1957 and 1966.

The purpose of this study was to assess the influence of influenza on the mortality from heart diseases and chronic lung diseases (HDCLD), especially in those over 70 years of age. From former analyses it was found that the highest mortality was in this age-group. Due to lack of data, a limit of 70 years of age was used rather than 65 years.
Because the relationship between influenza and a particular cause of death from HDCLD is unknown, it was decided to include all causes of death from HDCLD.

The model used is not based on the classic epidemic-threshold model of Serfling, who used a linear term describing secular trend with sine and cosine terms describing seasonal
change[5-7].

Instead we used a regression model in which the observed monthly mortality from HDCLD (influenza not included) in people over 70 years is explained with a year variable, a month variable and the overall number of influenza-mortality cases, and assumes that monthly mortality has a Poisson distribution.

As part of this analysis it was important to quantify the underreported effects of the epidemics of influenza on mortality in elderly people. The period 1967-82 was chosen because there were major influenza epidemics until 1979, in contrast with the period from 1979 onwards in which only minor influenza epidemics occurred.

Materials and Methods

We assume that variations in mortality from HDCLD (influenza not included) in people over 70 years depends on three variables. The main objective was to estimate the relationship between this HDCLD mortality among the elderly and the influenza mortality-rate in the total population, taking yearly and seasonal effects into account. Having developed the model, the next step is to eliminate the effects of influenza on it. This is done in the model by setting the influenza activity to zero while leaving the yearly and monthly effects the same. The difference between the predicted mortality from HDCLD in the situation of normal (i.e. observed) influenza-activity and the predicted mortality in the absence of influenza activity is defined as the excess mortality in people over 70 years of age.

The measure of influenza activity is the overall influenza-mortality in all ages (International Classification of Diseases (ICD), 9th revision: AM 34) (primary cause of death) per month given by the Dutch Bureau of Statistics during the period January 1967 to December 1982[8], expressed per million population. The causes of death included under HDCLD are summarized in table 1.

Table 1. Causes of death used in the study according to the International Classification of Diseases (ICD), 7th, 8th and 9th edition.

AM 26	Chronic rheumatic heart diseases
AM 27	Hypertension
AM 28	Acute myocardial infarction
AM 29	Other ischaemic heart diseases
AM 30	Cerebrovascular diseases
AM 31	Arteriosclerosis
AM 32	Other diseases of the circulatory tract
AM 33	Pneumonia
AM 34	Influenza
AM 35	Bronchitis, emphysema and asthma

During an observation period of 16 years (=192 months) the monthly observed number of mortality cases from all causes of HDCLD (table 1) except influenza, is assumed to have a Poisson-distributed random variable with mean and variance equal to a parameter λ specified as:

$$\lambda_i = N_i \cdot \exp_{j=1}^{12} \left(\sum_{k=2}^{16} \alpha_j M_j + \sum \beta_k J_k + \gamma F_i \right)$$

i = 1,...,192 (monthly figures over the years 1967-82)
N_i = population size above the age of 70 in month i
M_j = 1 for calendar month j
= 0 elsewhere j=1,...12 (January - December)
J_k = 1 for calendar year 1966 + k
= 0 elsewhere k = 2,...,16 (basis year = 1967)
F_i = influenza rate in month i (per million in all ages)

In this model λ_i is the expected number of HDCLD (influenza not included) deaths above the age of 70 in month i. F_i is the rate of influenza deaths (influenza-activity-indicator) per million per calendar month in the total population. α, β and γ are the coefficients to be estimated. Special interest lies in coefficient γ which represents the effect of the influenza rate in the total population on mortality from HDCLD among elderly people (>70). The quantity 1-exp ($-F_i$) represents the excess mortality in month i as a proportion of λ_i. The model also specifies that the expected number of mortality cases above 70 is proportional to the total population size N_i above 70.
The coefficients α, β and γ are estimated by a Poisson regression analysis with the natural logarithm of N_i as offset. The Generalized Linear Interactive Modelling (GLIM) system[9-10] was used.
The assumption is made that the monthly observed numbers of mortality cases are mutually independent, given the explanatory variables year, month and influenza-rate.

Results

The time series of monthly observed mortality and predicted mortality (influenza not included) for the HDCLD (in people over 70 years per thousand) are presented in Fig. 1. It is obvious that the predicted mortality correlates well with the observed mortality.

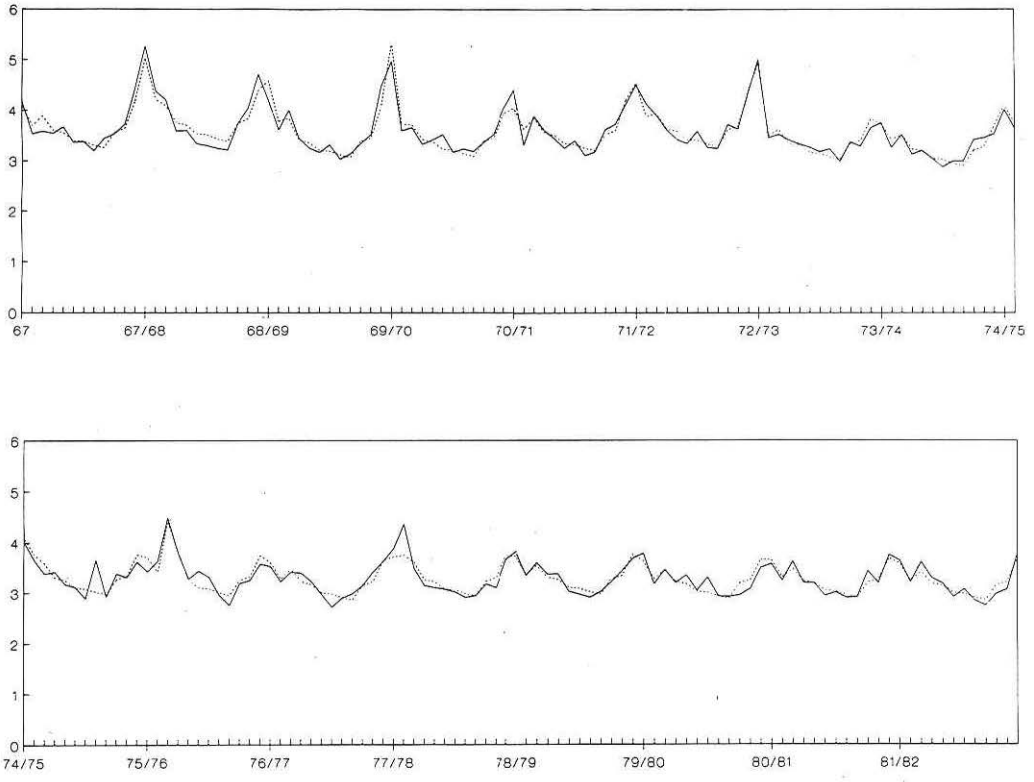
With the model the effect of an increment in the monthly influenza rate with one per million is estimated. This increment is equivalent to an additional 14 influenza mortality cases in the total Dutch population of 14 million. The resulting effect is an increase of 0.53 % (see Table 2) in the monthly number of 3000 to 4000 HDCLD deaths in the population above 70 years, an absolute number of 16-21 deaths. Hence, each additional influenza death in the total Dutch population 'generates' 1-1.5 deaths from HDCLD among the elderly as calculated with the model.

We can now calculate with the aid of the model the excess HDCLD deaths (>70 years) and compared this figure with the observed influenza mortality in this age group. The results are represented in Table 3. It can be concluded that if one influenza death occurred in the elderly 1,5-2 deaths in HDCLD are associated with this one influenza death. Thus, the total impact of influenza in people above 70 years is almost 200% higher if we take account of HDCLD.

One can also predict mortality while supposing that influenza activity is nihil. In Fig. 2 the time series of predicted mortality (per thousand influenza not included, in people over 70 years) is compared with and without the explanatory effect of influenza mortality. As can be seen, around January when influenza activity is at its peak, the difference between mortality with and without influenza activity is greatest.

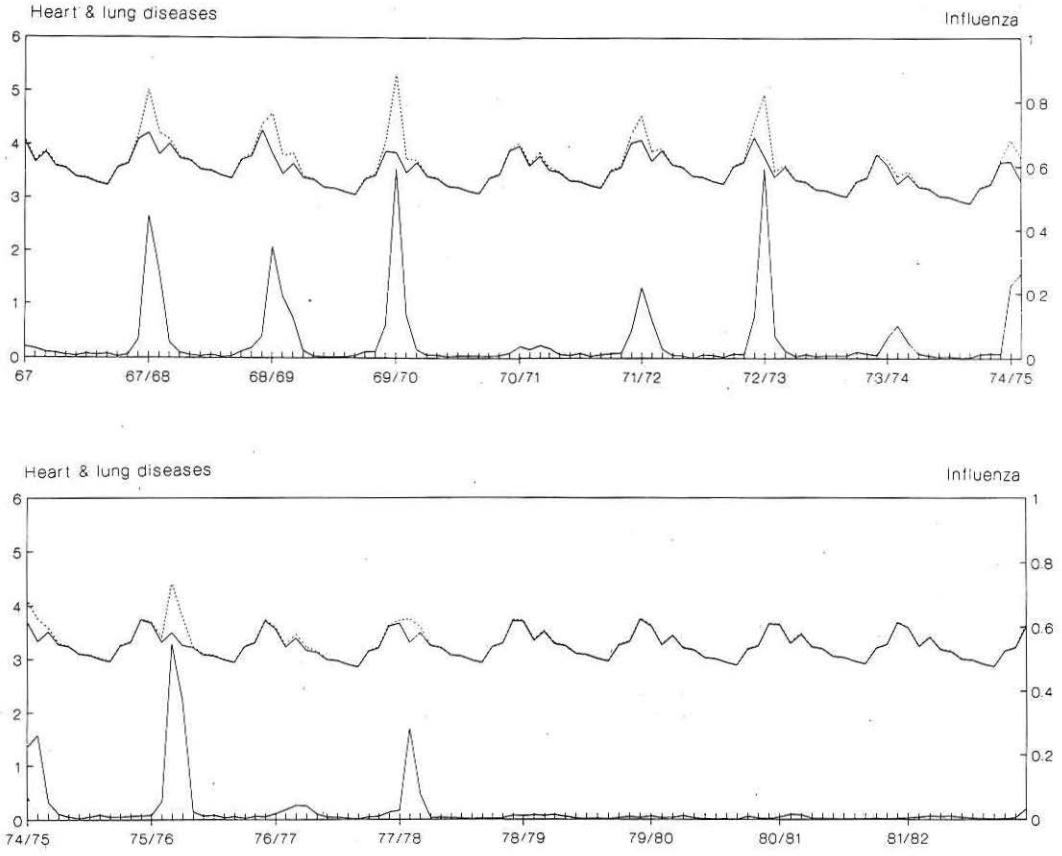
In Table 2 the results based on the estimated coefficients α, ß and γ, and their 95% confidence limits are presented. Also the deviance is calculated, from which it can be concluded that there is a greater difference compared to the theoretical Poisson variation[11]. This means that there are obviously more influential variables than those included in the model and that the estimated confidence intervals might be too narrow. The estimated effects of calendar year (as given by the ß coefficients) are not listed in Table 2.

Fig. 1 Monthly observed mortality and predicted mortality (influenza-deaths not included) from HDCLD per 1000 persons > 70 years in The Netherlands.



—— observed mortality from HDCLD
---- predicted mortality from HDCLD.

Fig. 2 Monthly predicted mortality (influenza deaths not included) with and without the explanatory effect of influenza mortality per 1000 persons > 70 years in The Netherlands.



Baseline: influenza mortality
------ predicted mortality from HDCLD with influenza activity
—— predicted mortality from HDCLD without influenza activity.

Table 2 Estimated number of deaths HDCLD per thousand in people over 70 years and 95% confidence limits, using a Poisson regression analysis in the model specified in the section Materials and Methods.
The estimated effects of calendar year are not listed in this table.

Variable	Estimated deaths/10^3	95% confidence limit	
January	4.046	4.075	4.107
February	3.654	3.596	3.679
March	3.853	3.800	3.906
April	3.589	3.539	3.639
May	3.549	3.500	3.599
June	3.390	3.342	3.438
July	3.369	3.322	3.417
August	3.293	3.247	3.340
Sept.	3.241	3.195	3.287
Oct.	3.564	3.514	3.613
Nov.	3.636	3.586	3.686
Dec.	4.099	4.044	4.155
Infl-r.	5.344*	5.166	5.522

Deviance 1098 (D.F.=164)
*Additional number of deaths per 1000 when the monthly influenza rate increases with one per million.

Table 3 represents HDCLD deaths and influenza deaths in people over 70 and the influenza-associated deaths per million. The prevalent viral strains are listed and the figures are given per "season" years: July 67-June 68, July 68-June 69, etc.

In 1957 the A(H2N2) strain occurred for the first time. In the following 7 years this Asian influenza was responsible for excess deaths. The last epidemic (1967-68) was the most severe[12] and was associated with 2380 deaths (see Table 3).
The subtype A(H3N2) virus (Hong Kong virus) which appeared in the Far East in the middle of 1968 circulated in Europe unchanged for four successive winters causing variable amounts of damage[13]. The first (1968/69) and second (1969/70) outbreaks were associated with high morbidity and mortality. The third period (1970/71) gave little mortality and the last (1971/72) mild mortality. Foy and colleagues[14] found the same pattern of these influenza epidemics in Seattle (USA). It can be concluded that 7500 deaths per million in people with HDCLD and above 70 years of age were associated with the Hong Kong epidemics in The Netherlands in the period 1968-1971.

Table 3. Observed HDCLD deaths (influenza not included), observed influenza deaths, estimated influenza-associated deaths in people over 70 years, per million in The Netherlands, and the prevalent viral strains.

Year	HDCLD deaths*	Infl. deaths*	Infl. ass. deaths**	Viral strains at large
1967/68	46140	898	2376	A/Asian(H2N2)
1968/69	43954	827	2388	A/HK/(H3N2)
1969/70	43366	929	3046	A/HK/(H3N2)
1970/71	42518	206	525	A/HK/(H3N2)
1971/72	44132	529	1496	A/HK/(H3N2)
1972/73	43890	886	2526	A/Eng/(H3N2)
1973/74	39698	307	780	A/PortC/(H3N2)
1974/75	40053	621	1645	A/PortC/(H3N2)
1975/76	41752	1083	2761	A/Vict/(H3N2)
1976/77	38730	206	522	A/Vict/(H3N2)
1977/78	39801	454	1157	A/Tx/(H3N2)A/USSR/(H1N1)
1978/79	39347	91	234	A/Tx/(H3N2)A/USSR/(H1N1)
1979/80	39240	63	157	A/Bank/(H3N2)
1980/81	38517	65	166	A/Tx/(H3N2)A/Bank/(H3N2)
1981/82	39113	58	144	A/Chile/(H1N1)
average	41350	500	1400	

*) Observed per million in people over 70 years.
**) Total influenza-associated deaths (influenza and HDCLD) per million in people over 70 y. HDCLD estimated from the model.

In the winter of 1972-73 a drift strain, A/England/72 (H3N2), caused an influenza epidemic[15]. This outbreak was associated with approximately 2500 deaths per million among elderly people. In October 1973 the A/England/72 virus was replaced by another variant, A/Port Chalmers/73. The number of deaths related to this influenza strain was approximately 800 in that year and 1700 in the next year. The A/Victoria strain of 1975/76 caused a high mortality and was associated with 2800 deaths. At the end of 1977 the old influenza A (H1N1) subtype reappeared[16]. The same subtype had already circulated in the world for 10 years between 1947 and 1957. This virus was associated with a low mortality: around 1200 persons > 70 years in the winter of 1977-78. There were no influenza outbreaks between 1979 and the end of the study period (1982), although influenza circulated in every winter period[17].

Discussion

Months with high influenza mortality match fairly well and proportionally with peaks in death from HDCLD in elderly persons (> 70 years), after adjusting for trend and seasonal effects. Although there is no definite proof of a causal relationship between influenza and excess mortality, it is clear from the estimates and figures that there is a strong association between death from influenza and HDCLD. The possible existence of a third unknown factor, which affects both mortality from influenza and mortality from HDCLD cannot be discarded with certainty. However, this concept is not corroborated by the absence of real influenza activity from 1979-82 and a corresponding lack of excess mortality from HDCLD during the same period. It is usually thought that cold weather has an adverse effect upon people, sick or well, and many studies[18] have shown that excess mortality occurs when the weather is very cold. This 'cold-weather' hypothesis has been challenged by Anderson & Le Riche[19] who, in comparing Ontario with England and Wales found that, while the seasonal variations in temperature were greater in Ontario, the seasonal variations in chronic heart disease (CHD) mortality were greater in England and Wales. They suggested that in stead of temperature, the increase in respiratory infections which occur in winter could be responsible for the rise in CHD mortality. Their hypothesis was supported by the increase in mortality due to cardiovascular disease during influenza epidemics in subsequent years[20]. In 1976 Rogot and his colleagues[21] examined the daily variation in USA mortality. Their results clearly point out daily as well as seasonal and yearly similarities and differences in mortality, but the most significant sporadic factors affecting mortality appeared to be influenza and the unusually hot weather in July 1966.

Bainton and co-workers[22] tested the hypothesis that the number of deaths from ischaemic heart disease is greater at the time of an influenza outbreak, allowing for any effects of temperature. Their data demonstrated an increase in the number of deaths during such outbreaks. Examination of these data for age provided a consistent support for the hypothesis in those aged over 55 years.

If respiratory agents are indeed responsible for the rise in HDCLD, it is important to identify these agents. In winter some viruses may become more active; for instance rhinoviruses, coronaviruses and parainfluenza viruses. These viruses are generally thought to cause common colds and are rarely a cause of severe illness. Respiratory syncytial virus and Mycoplasma pneumoniae can be especially important in children and elderly people. However, these agents cause epidemics every winter and were included in our model.

In this study we made no allowance for the fact that some elderly persons have been vaccinated and are thus protected against influenza. No correct figures on the numbers vaccinated are available. Therefore, this aspect was not included.

It has been suggested that influenza-related deaths occur in patients who would soon have died from other underlying illness. However, Fig. 1 does not show a decline in the number of deaths following a period of high influenza-associated mortality.

Tillet and colleagues[23] examined the other possibility that in winter influenza deaths could be followed by a deficit in summer deaths but could not find a correlation, nor could they demonstrate that high level in excess deaths in one winter tended to be followed by a deficit in the next winter. These observations suggest that excess deaths attributable to influenza are not only shortening lives by a few months.

This data from this study suggest that 1400 deaths, per year per million people over 70 years of age were due to influenza during the study period of 16 years. Put in another way in The Netherlands two HDCLD deaths in people over 70 years were associated with one influenza death in the elderly.

Barker & Mullooly[24] calculated in 1980 that the excess mortality for the epidemic of 1972/73 was around 1000 deaths per million people over 65 years of age. They compared the morbidity and mortality of two epidemic years with a non-epidemic year. The number of excess deaths in their study is less than in ours. We have used a model to forecast the mortality based upon the influenza-mortality, using a trend variable and season variable, while Barker & Mullooly simply compared two different periods. Alling and colleagues[25] used deaths from influenza and those from acute respiratory diseases as indicators of influenza. They estimated an excess annual death rate of 500 among people over 65 years of age for the period 1968-1976.

Influenza has a larger impact on mortality than just those cases whose cause of death is listed as "influenza". The most likely explanation for this underreporting is the well-known imprecision in identifying the cause of death. Mortality from influenza as the major underlying cause may easily be listed under 'heart' and 'lung' categories in elderly people (over 70 years) already suffering from HDCLD. In future this will become more important because the proportion of people over 60 years will increase to 25 % of the population in the USA by the year 2020[26].

More research is needed on the causes of morbidity and the possible role of influenza in causing excess mortality from heart diseases and chronic lung diseases.

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Influenza and Influenza Related Mortality, 1967-1989

Introduction

In chapter 1 the influence of influenza on the mortality from heart and lung diseases, in people over 70 years of age was assessed. Heart & lung mortality is tried to be explained with four variables: a) influenza activity, b) month, c) year and d) population size.

The outcome suggested that per year 1,400 deaths per million people over 70 years of age were due to influenza, in the studied period 1967-1982. It could be concluded that one influenza death in the population above 70 years, "generated" almost two deaths diagnosed as heart and lung diseases in the elderly.

In this study the total impact of influenza will be estimated over a longer period (22.5 years), and also in other groups regarding age and disease entity. This means that the total population (all ages) and total mortality (all death causes but influenza) will be considered. At the outset death causes will firstly be divided into three main diagnostic categories:

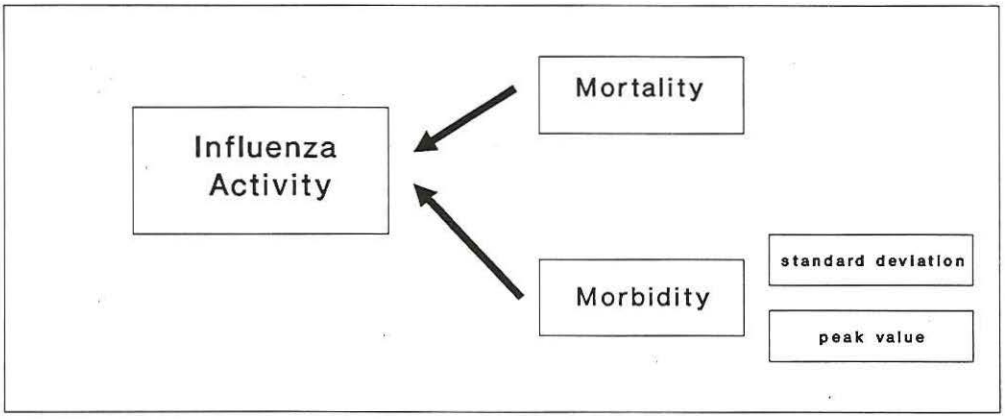
1. heart disease
2. lung disease
3. other death causes

Two main categories are further subdivided namely deaths due to heart diseases into five death causes and deaths due to lung diseases into two death causes. Also ages will be subdivided, namely into four age groups: 0-59 years, 60-69 years, 70-79 years and 80 years and over.

This study tries to attain five objectives:

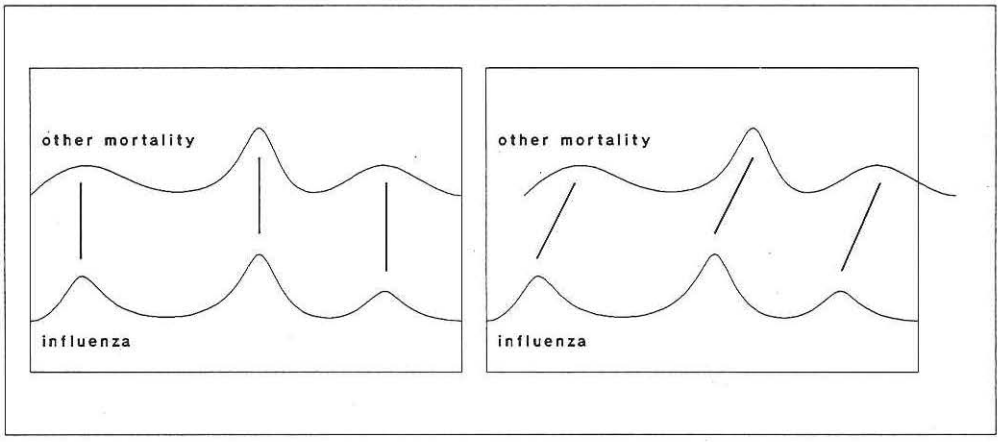
1. Influenza-activity has been defined so far as the influenza mortality rate in the total population. A better-indicator for influenza-activity might be influenza morbidity. In the first section three influenza-activity indicators and their combinations are compared with the object to choose the most effective (i.e. related) indicator for the new model (see figure 1).

Figure 1 Illustration of influenza-activity



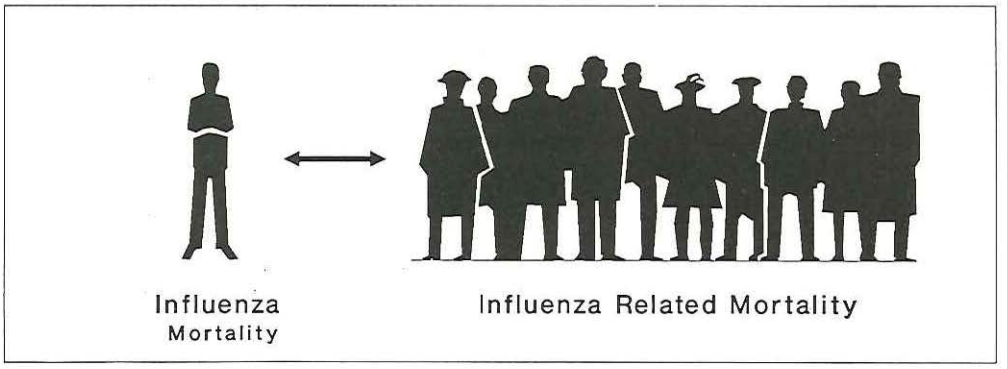
2. In the second section the effect of a possible time-lag is considered. It is not unrealistic to assume that there is a time delay in the relationship between influenza activity and excess mortality; the effect on excess mortality might be observed about one month later than the influenza activity as its potential cause (see figure 2). Hence in the second section a model will be considered in which the influenza activity indicator has a time lag of one month. Theoretically there may be more or less than one month time-lag. For the moment we restrict our study to one month-time lag as a first approximation. Moreover, less than one month time-lag was not feasible, since our time unit is a month.

Figure 2 Illustration of time lag. In the first graph the effect of the lowest line is at the same time visible in the upper line, in the second graph the effect is delayed.



3. Depending on the results obtained in sections 1 and 2 a tentative regression model will be fitted in section 3. On the basis of this model the influenza/excess mortality ratio will be estimated. This ratio represents the number of influenza related deaths for one registered influenza death. Influenza related mortality will be analyzed separately within each age group (see figure 3).

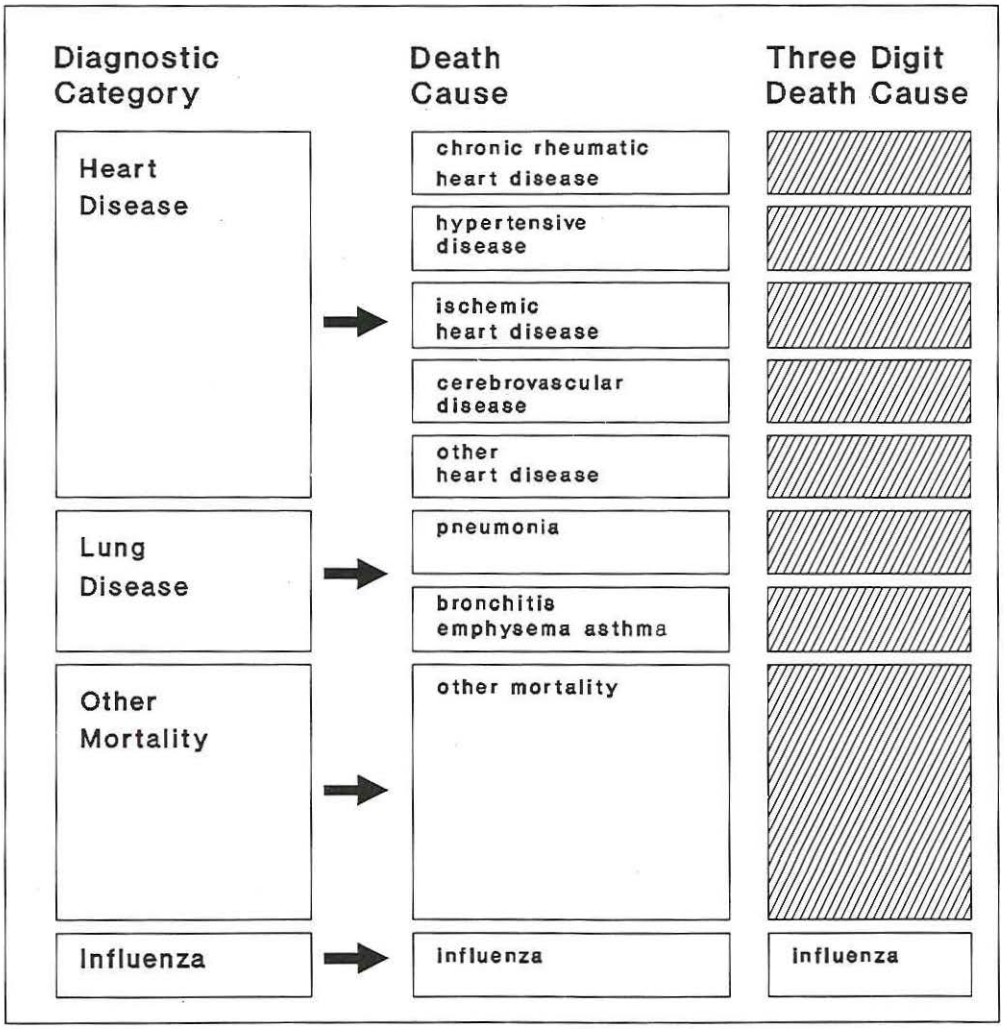
Figure 3 Illustration of influenza and influenza related mortality calculated using the model.



4. In section 4 influenza related mortality is examined within each diagnostic category, i.e. heart-, lung-, and other mortality categories within each age group.

5. In section 5 influenza related mortality will be considered separately for each subdivision of death causes within an age group. Heart mortality being subdivided into five death causes, and lung mortality into two death causes (see figure 4).

Figure 4 Structure of studied population



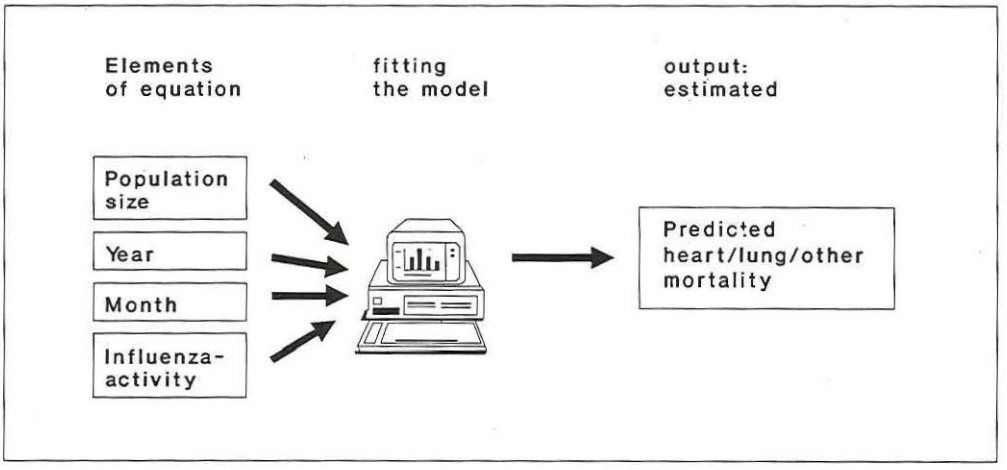
Materials and Methods

It is tentatively assumed that the time series of mortality from a certain cause (influenza not included) in a certain subpopulation (e.g., an age group) can be explained with four explanatory variables: population size, year, month and an influenza activity indicator in the total population.

The main objective is to estimate the relationship between mortality and the influenza activity in the total population, taking into account yearly and monthly (seasonal) effects (see figure 5). Having estimated the parameters in the model, the next step is to eliminate the effects of influenza from the fitted model. The predicted basic mortality is calculated from the model by setting the influenza activity at zero while leaving the yearly and monthly effects the same.

The difference between the predicted normal mortality i.e. in the situation of normal (observed) influenza-activity and the predicted basic mortality in case of absent influenza activity is defined as the excess mortality.
According to the general underlying model presented in chapter 2 the parameters will be estimated using the GLIM procedure in a similar way [1] [2] [3](see for details Appendix Statistics formula 1). This means estimation of the coefficients α (month effect), ß (year effect) and γ (influenza-activity) in this model. Special interest lies in the coefficient gamma which represents the effects of the influenza activity in the total population on mortality from a certain cause (other than influenza) in a certain subpopulation (see Appendix Statistics formula 2 and an example of fitting the model by the GLIM-procedure is shown in the Appendix GLIM procedure).

Figure 5 Illustration of the computer model



As a first approach to measure influenza-activity, this is defined as the monthly influenza-mortality rate (International Classification of Diseases (ICD), 9th revision: AM 34) (primary cause of death) as given by the Dutch Central Bureau of Statistics during the period 1-1967 to 6-1989 in the total population (all ages). In sections 1 & 2 of the results this influenza-activity indicator will be examined.
In first instance the model is only specified for one death cause category and only one subpopulation (age group) considered. In order to indicate the various death cause categories and subpopulations (age groups) two more indices are necessary, one for death cause category and one for subpopulation (see Appendix Statistics).

In this chapter there are three diagnostic categories and each category comprises of a number of death causes (see Appendix Classification). The measure of mortality is the observed number of death cases per month in a diagnostic category in the subpopulation (age-group) considered.

The three diagnostic categories are:

1. heart disease
2. lung disease
3. other mortality

The diagnostic category of heart disease is subdivided according to the International Classification of Diseases (ICD) into five death causes:

1. chronic rheumatic heart disease
2. hypertensive disease
3. ischemic heart disease
4. cerebrovascular disease
5. other heart diseases

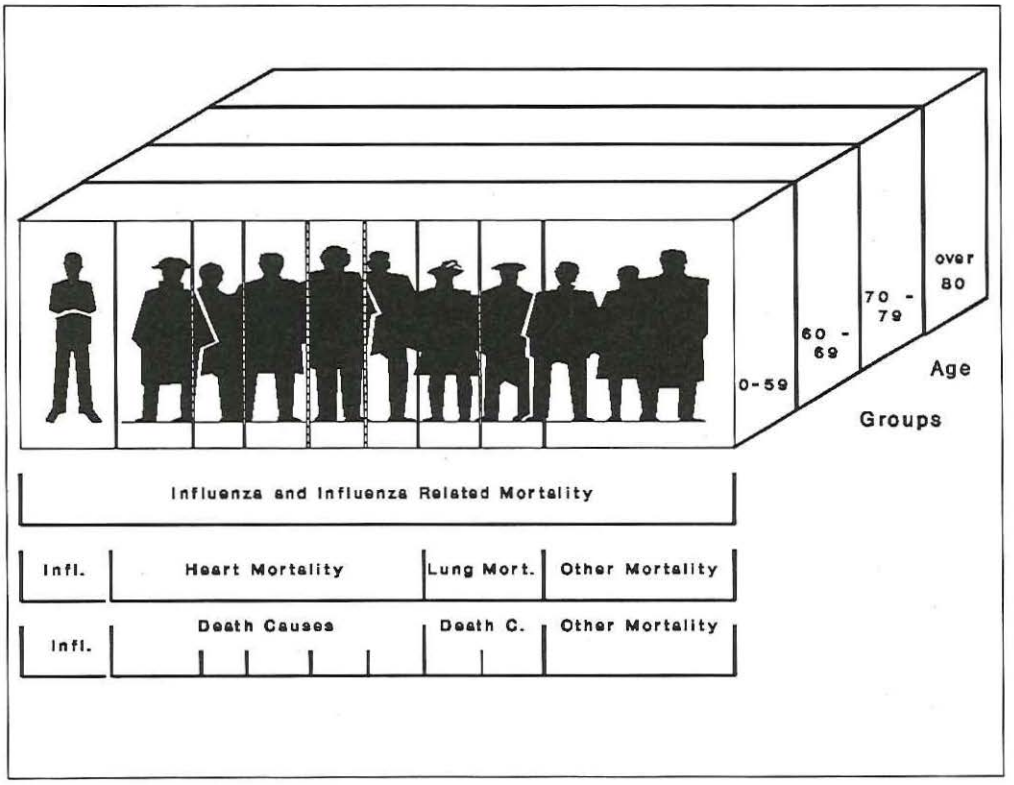
The diagnostic category of lung diseases is subdivided into two death causes:

1. pneumonia
2. bronchitis/emphysema/asthma

Obviously, each death cause as mentioned above consists of a number of so-called "three digit death-causes" from the system of International Classification of Diseases (ICD). The "three digit death causes" are the most refined level of classification (see figure 6). In the period studied three versions of the ICD were used: 7th 1959-1968, 8th 1969-1978, 9th from 1979. In the different versions not every death cause consists of the same set of "three digit death-causes". For some diagnostic categories it is not possible to keep the classifications perfectly matched over time (see Appendix ICD). The extent to which this might seriously affect the results will manifest itself through the effect of the year factor in the model.

The observation period is 22.5 years (=270 months): January 1967 to June 1989. So there are 270 so called "design points" with correspondingly 270 observations to estimate 35 parameters (12 month effects, 22 year effects and 1 influenza effect).

figure 6 Illustration of diagnostic levels



Results

section 1: Influenza-activity indicator

Parameter estimates of a hypothesized model are obtained by maximizing the log likelihood with respect to the parameters. A theoretical maximum of the log likelihood is achieved when there is an exact fit in which the fitted values are equal to the observed data. Hence, the distance between the theoretical maximum of the log likelihood and the maximized log likelihood is a measure for the goodness-of-fit of the estimated model. Actually, twice that distance is used as a measure for goodness-of-fit and is called "scaled deviance"[4].
This measure will be used to test the goodness-of-fit of a hypothesized model to the data. Under the hypothesis that the observed number of mortality cases in a month is indeed a Poisson variate with mean and variance equal to a parameter labda, the scaled deviance follows approximately a chi-square distribution having number of degrees-of-freedom equal to the total number of design-points with an observation (i.e. months) minus the number of parameters estimated, here: 270 -35 = 235. An extreme high value of the scaled deviance, i.e. in the upper 5% tail of its chi-square distribution, warrants the conclusion that the model does not fit well enough. There is overdispersion (or extra-Poisson variation) in the data, possibly due to either extra random variability or unobserved heterogeneity caused by (unknown or unobserved) explanatory variables not incorporated into the model. Since the scaled deviance is proportional to the underlying monthly number of mortality cases and the population sizes, scaled deviance scores can become extremely high even if there are small model violations in a situation with very large values at some design points, as is the case here in some of the analyses.
However, if heterogeneity is due solely to extra random variation, the parameter estimates are still valid. Only the standard errors of the estimated parameters would be biased downward. A correction factor for the underestimated standard error is obtained as the square root of the ratio of the scaled deviance to its number of degrees-of-freedom[5].

Mortality from heart diseases and other diseases is influenced by many factors. For example, by season: in winter mortality is higher than in summer. To take this seasonal effect into account the calendar month is an explanatory factor in the model. But the type of weather could also have an impact on mortality. The problem with this factor is that it cannot be represented by one monthly figure. There are several weather indicators e.g. temperature, humidity, and there are several ways of summarizing each indicator into one monthly figure, e.g. mean, median, minimum and maximum. So it is too difficult to take the factor "weather" into account properly. We consider that a part of the factor "weather" will be represented by the month factor.

Influenza activity may also be represented in different ways, by influenza mortality, morbidity or both. In chapter 4 the relationship between mortality and morbidity will be investigated. In this section three parameters together with their combinations will be introduced and examined with respect to their capacity to predict influenza related mortality:

I monthly influenza mortality
II maximum number (peak-value) from the weekly figures of influenza-like illnesses over a season-year
III standard deviation of weekly figures of influenza-like illnesses over a season-year
IV the combination of (I) and (II)
V the combination of (I) and (III).

The combination of II and III is not done because they are closely correlated.
The parameter or combination of parameters with the lowest "scaled deviance" has the best capacity of predicting the influenza related mortality. In table 1 the results are presented.

Table 1 scaled deviance, as a measure of goodness of fit of a model including various influenza indicators (using the GLIM-procedure)

Indicator	scaled deviance and degrees of freedom
(I) monthly influenza mortality	1690 (196)
(II) peak number of influenza-like illness (ILI)	2471 (196)
(III) standard deviation of weekly numbersILI	2471 (195)
(IV) combination I & II	1668 (195)
(V) combination I & III	1668 (195)

From table 1 it follows that influenza mortality alone is a better indicator (lowest scaled deviance) than the two morbidity measures. The combination is scarcely better and besides it would complicate the interpretation of results, because influenza activity then would have to be quantitated as a somehow weighted average of two indicators.
Therefore in the next sections, **influenza activity** in the regression models used throughout will be defined as **monthly influenza-mortality.**

section 2: Time-lag in the relation between influenza and related mortality

Influenza could be the trigger for other mortality. In such a causal relationship, it can be expected that the cause precedes the effect it produces. Suppose that influenza causes excess mortality in heart diseases but that the effect would be visible only about one month later. In that case the influenza related mortality reacts with a time-lag of one month on influenza activity.
If there would be a time-lag of one month, the relationship between influenza related mortality and influenza-activity occurring one month earlier, would show a better fit in terms of the "scaled deviance" than the influenza-activity in the same month.
To consider this phenomenon it is not sufficient to look only at "total mortality (excl influenza)" as the dependent variable. It is conceivable that a time-lag occurs only for certain death causes. For example, a time-lag would be more likely concerning chronic rheumatic heart disease than for pneumonia. So it is necessary to study this phenomenon for each death cause separately. In table 2 the goodness-of-fit results in terms of scaled deviances when using the influenza-activity as a predictor with and without one month time-lag are compared for each death cause.

Table 2: Goodness-of-fit in terms of scaled deviances when using the influenza-activity as a predictor with and without one month time-lag are compared for each death cause

dependent variable	scaled deviance	
	without (df=235)	1 month time-lag (df=234)
total mortality (excl. influenza	2070.7	3246.6
chronic rheumatic heart disease	314.8	316.2
hypertensive disease	275.4	299.6
ischemic heart disease	722.4	950.6
other forms of heart disease	927.7	1225.1
cerebrovascular disease	602.2	705.6
pneumonia	1597.7	2345.3
bronchitis, emphysema and asthma	625.8	1076.7

From table 2 it is clear that a one month time-lag in all instances worsens the "goodness of fit" of the regression model. The conclusion is that an effect of influenza-activity if any, on other mortality generally will occur in the same month. In theory it is conceivable that the time-lag could be more than one month. From previous experience, however a time-lag of one month is to be considered as most plausible (see section Conclusion & Discussion).

section 3: Ratio Influenza mortality and Influenza Related Mortality

In the previous sections we found that the best fit of the model so far is achieved with the use of synchronous influenza mortality without time-lag as explanatory variable. The monthly overall mortality (excluding influenza) will now be modelled with four explanatory variables: monthly influenza mortality, calendar month (to take into account the season), calendar year (long-term effects) and population size. The result of fitting this model is represented in figure 7, where observed mortality is compared with mortality predicted from the regression model. It can be seen that the model fits fairly well. Figure 7b shows the Z-scores of the residuals, it can be seen that they are randomly distributed.

figure 7 Observed and predicted total mortality (excluding influenza) in the period 1967-1989 in The Netherlands. Black line: observed mortality; Red line: predicted mortality.

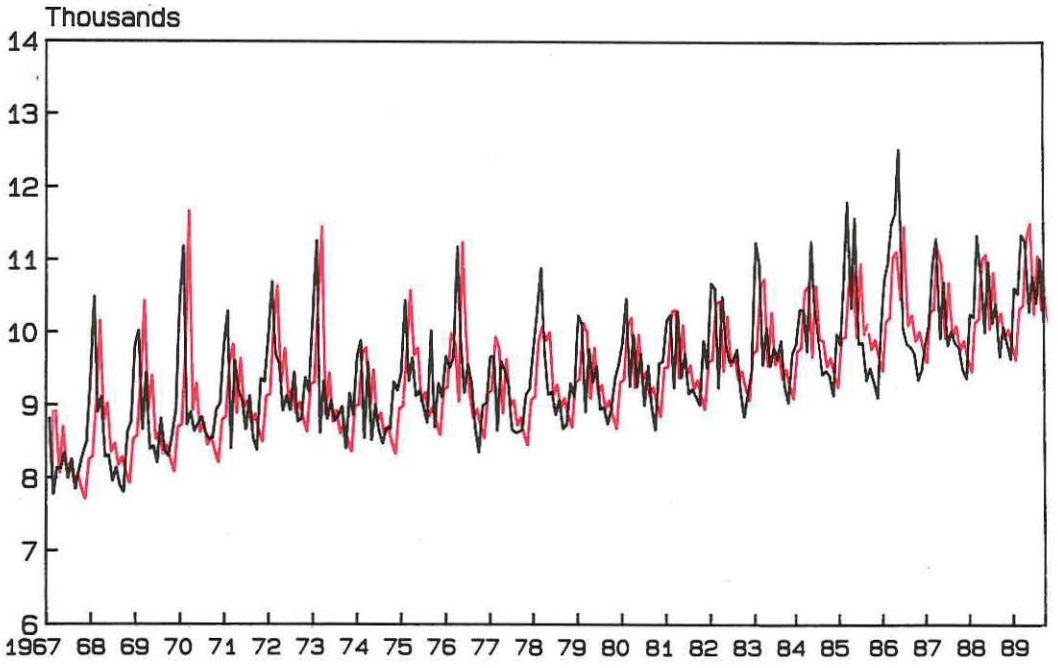
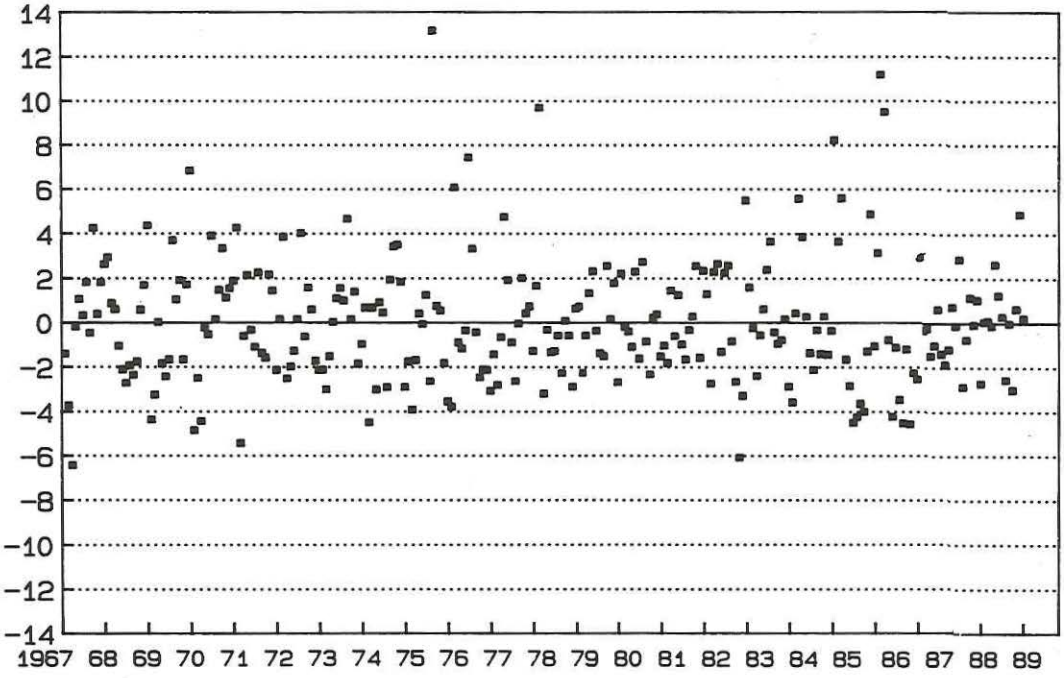
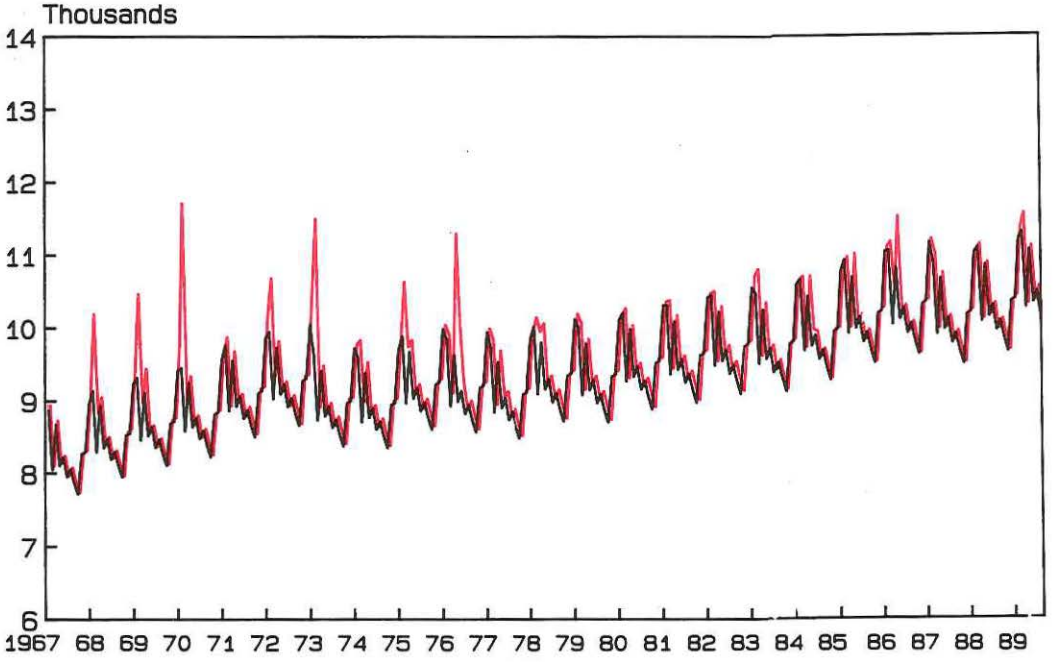


Figure 7b Z-scores of the residuals of the total mortality (influenza excluded) per month.



The next step is to simulate a situation without influenza-activity by eliminating the influenza-activity. In figure 8 the line represents the predicted situation with normal influenza activity present, the dotted line simulates the situation when influenza activity is absent. In a number of periods there is a clear difference between both predictions.

figure 8 Predicted total mortality (excl. influenza) assuming presence or absence of influenza activity.

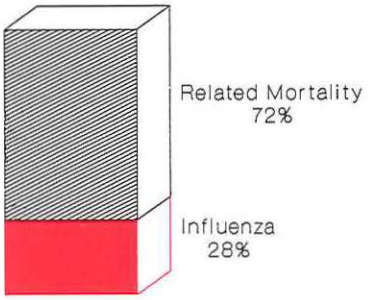


red line: influenza activity present
black line: influenza activity absent

Next step is to consider how many deaths are related to influenza on the basis of our model. We calculated for the whole period studied (22.5 years) that the number of registered influenza deaths equal in The Netherlands 9710 (see Appendix Statistics formula 3).
We estimated the number of excess deaths associated with influenza activity to be 25101 (formula 4).

This result means that in this case the ratio of influenza mortality / influenza related mortality is 2.6 (25,101 / 9,710. This can be interpreted as follows. For every influenza death registered by the Dutch Central Bureau of Statistics, about 2.6 other deaths are associated with this influenza death. So the effective impact of influenza on mortality is greater by a factor of about 3.6 (figure 9).

figure 9 Influenza mortality and influenza related mortality in total population



The next step is to estimate the proportional distribution of excess mortality over various age groups.
The excess mortality within an age group can be estimated using the regression model for subpopulations (age groups). (formula 5).
From table 3 it appears that about 5% of the influenza related deaths occurs in people under 60 years, 50% between 60 and 80, and about 45% in people over 80 years.

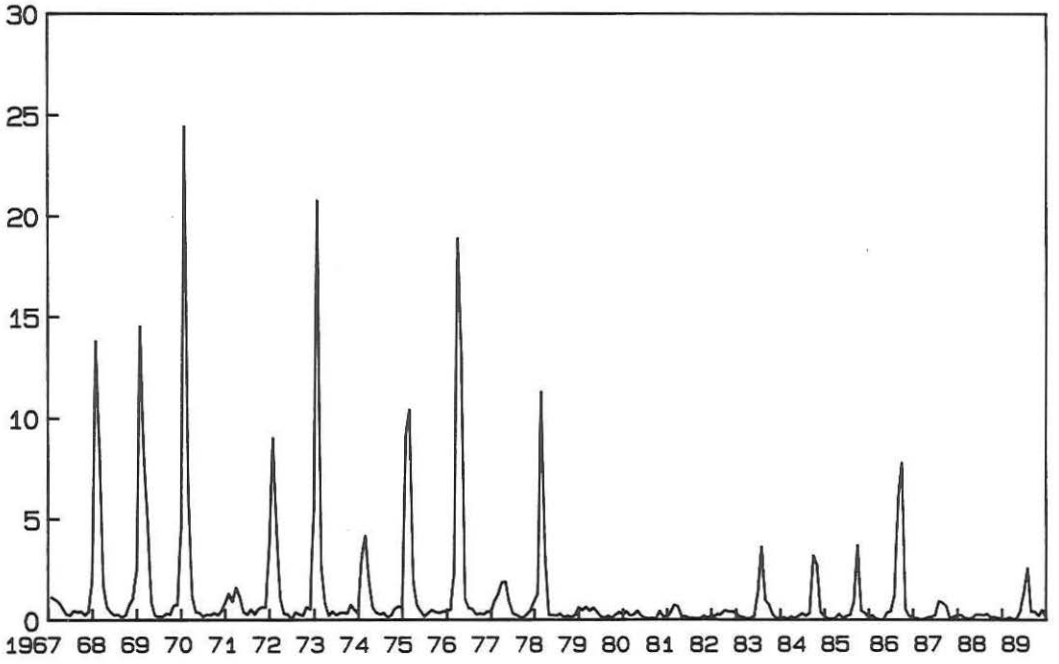
Table 3 Influenza related mortality by age group

age (yr)	estimated number	%
0 - 59	1190	5
60 - 69	4409	18
70 - 79	8660	35
over 80	10841	43
total	25101	100

Influenza mortality and influenza related mortality is especially important in winter season during epidemics (with some exceptions e.g. Asian flu). The next step is therefore to derive the part of total mortality per month that is associated with influenza. This equals the predicted total influenza mortality and influenza related mortality as proportion of predicted total mortality (formula 6 & 7).

Figure 10 shows the influenza mortality and influenza related mortality per month as a percentage of the total mortality (influenza included) in that month. In some months this can be more than 24%. In other words in that particular month 24% of the total mortality is associated with influenza.

figure 10 Influenza mortality and influenza related mortality as percentage of total mortality by month



In table 4 the excess (influenza related) mortality as percentage of total mortality (influenza included) is presented per season year per age group (formula 7).
The percentage of 0.99 is the average of all 22 season years in the total population (formula 8 & 9).

Table 4 percentage of excess influenza related mortality of total mortality per season-year per age-group

season-year	60-69y	70-79y	over 80y	tot.pop.
1967/68	1.82	2.26	2.66	1.95
1968/69	2.12	2.60	2.99	2.24
1969/70	2.80	3.47	4.12	2.98
1970/71	0.46	0.56	0.65	0.49
1971/72	1.31	1.62	1.87	1.39
1972/73	2.26	2.77	3.28	2.39
1973/74	0.74	0.91	1.05	0.78
1974/75	1.55	1.94	2.27	1.67
1975/76	2.57	3.15	3.63	2.71
1976/77	0.52	0.63	0.73	0.55
1977/78	1.10	1.39	1.63	1.19
1978/79	0.24	0.29	0.34	0.25
1979/80	0.16	0.19	0.22	0.17
1980/81	0.17	0.22	0.24	0.18
1981/82	0.15	0.19	0.21	0.16
1982/83	0.47	0.58	0.68	0.50
1983/84	0.47	0.57	0.66	0.50
1984/85	0.39	0.48	0.56	0.42
1985/86	1.04	1.28	1.51	1.11
1986/87	0.20	0.25	0.28	0.21
1987/88	0.10	0.12	0.14	0.10
1988/89	0.39	0.47	0.55	0.41
average	0.97	1.16	1.26	0.99

Table 5 shows excess (influenza related deaths) mortality per million inhabitants per age-group per season-year (formula 10).

Table 5 number of influenza related deaths (influenza mortality excluded) per million inhabitants within each age-group by season-year.

season-year	60-69y	79-79y	over 80y	tot.pop.
1967/68	363	1168	3859	159
1968/69	429	1354	4316	185
1969/70	575	1828	5975	250
1970/71	91	287	927	40
1971/72	261	852	2729	118
1972/73	445	1434	4752	201
1973/74	141	440	1443	63
1974/75	296	949	3152	136
1975/76	492	1560	5035	225
1976/77	97	298	938	44
1977/78	200	651	2109	96
1978/79	43	135	431	20
1979/80	28	87	279	13
1980/81	30	99	307	15
1981/82	27	82	270	13
1982/83	81	254	841	41
1983/84	80	250	823	41
1984/85	66	207	702	35
1985/86	175	555	1928	95
1986/87	33	104	354	18
1987/88	16	50	169	9
1988/89	63	197	674	35
average	183	584	1910	84

At present there are about 1.282 million people in the age-group 60-69. The average excess influenza related mortality is calculated as 183 per million per season year (see table 5). In this age-group, taking into account the population size of 1989, the expected total number of influenza related deaths is 235 (= 183 x 1.282). Similarly,the expected number in the age-group 70-79 is 494 (= 584 x 0.846) and in the age-group over 80 years equals 798 (= 1910 x 0.418). Total number of influenza related deaths in people over 60 years equals therefore 1527 (= 235 + 494 + 798). The actual number of deaths ascribed to influenza in people over 60 years is reported as 565[1].
The total impact of influenza is therefore to be estimated as about 2100 per season-year (the average of 22 season-years) in The Netherlands.

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[1] incidence of influenza mortality per million in the age groups 60-69y, 70-79y and over 80y is resp. 40, 167 and 891.

section 4: Influenza Related Mortality by Diagnostic Groups

In section 3 we found that according to the fitted model in the period 1967-1989 about 25,000 people were estimated to have died of causes associated with influenza in addition to 9710 influenza deaths. Most of these people were in the age group over 60 years. Apart from age the reported diagnosis may be an important factor. Four diagnostic categories will be distinguished here:

1. influenza
2. heart disease
3. lung disease
4. other mortality

In a similar fashion as we analyzed excess mortality by age group in section 3 (see for example table 3) we performed an analysis by diagnosis (see Appendix Statistics formula 11).
Figure 11 shows this subdivision of four categories. Apparently about 50% of the influenza related deaths is estimated to occur in the heart disease group and about 23% in the lung disease group. The remaining 30% are classified as other mortality (category 4).

figure 11 Influenza mortality and influenza related mortality by four diagnostic categories

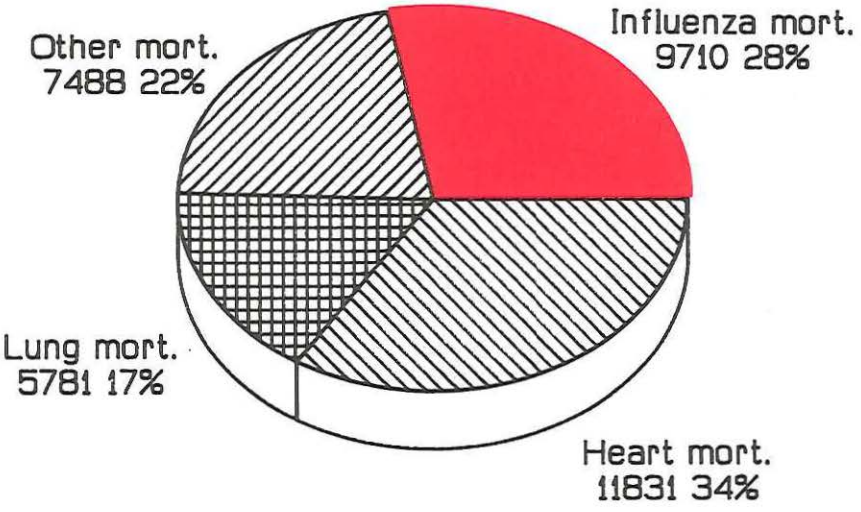


Figure 12 shows a further subdivision within each of the four age groups namely into all four diagnostic categories. Each bar from figure 12 represents the influenza & influenza related deaths per age-group. The age-group 0-59 years includes only 5% of these deaths. In people over 60 years there are no appreciable differences between the age groups.

figure 12 Total influenza mortality distributed by diagnostic category per age-group

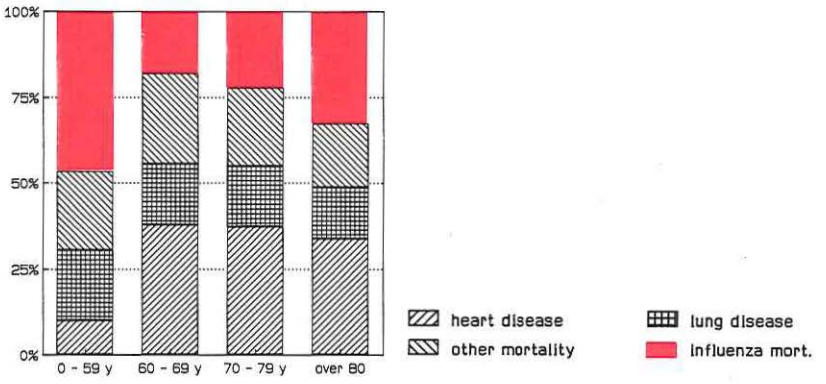
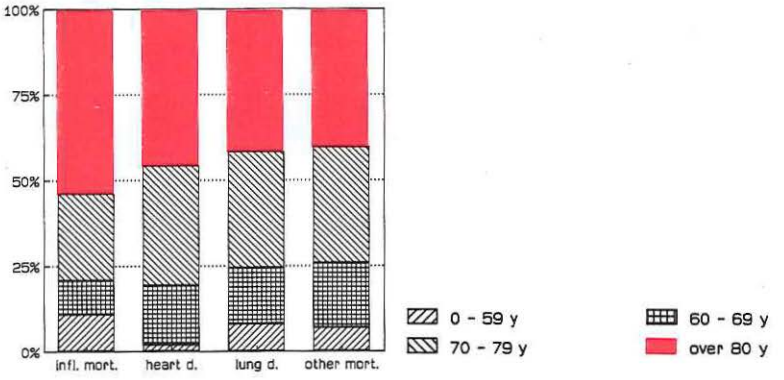


figure 13 Total influenza mortality distributed by age-group per diagnostic category.



The age-distribution (see figure 13) per diagnostic category shows that influenza deaths occur for about 11% in people under 60 years. For influenza related mortality, only 2% of people are under 60 years in the heart disease group and about 8 % in the lung disease group.
For every diagnostic category the majority of influenza related death cases occur in people over 80 years.

The analysis shows that for every diagnostic category the mortality occurs most in people over 60 years. There are no great differences in age-distribution of the diagnostic categories, this means that the majority of mortality in every diagnostic category occurs most in people over 60 years.

section 5: Death cause and influenza related mortality

The final step in this context is to analyze the data at the level of death cause. The main diagnostic categories are further differentiated into subcategories. The heart disease category is subdivided into 5 diagnostic subgroups.

1. Chronic Rheumatic Heart disease
2. Ischemic Heart disease
3. Hypertensive Heart disease
4. Other Heart disease
5. Cerebrovascular disease

Each subgroup will be reviewed in this section (see formula 2).
Every death cause mentioned above comprises a number of "three digit death-causes" from the system of International Classification of Diseases (ICD). The Appendix ICD shows the "three digit death-causes" concerned.

The excess mortality within a death cause group can be estimated using the regression model for subpopulations (death cause). The monthly overall mortality (excluding influenza) will again be modeled with four explanatory variables: monthly influenza mortality, calendar month, calendar year and population size. The result of fitting this model will be represented for every death cause. Next step is to mimic the situation when influenza is absent. The difference between the presence and absence of influenza in the model concerning the death cause will be the estimated excess mortality for that particular death cause.

Chronic Rheumatic Heart disease, (diseases of the valves, etc)
Figure 14 shows the observed mortality registered as chronic rheumatic heart disease and the predicted mortality on the basis of the fitted model. It is evident that mortality for this cause increases until 1973, and decreases from 1976. Either the incidence has really decreased or the change in classification is the reason. The incidence is (from 1980 onwards) between 20 and 40 per month in The Netherlands. The observed mortality fits fairly well with the predicted mortality. Figure 15 shows the percentage of the chronic rheumatic heart disease that is estimated in the model as being associated with influenza mortality in that particular month. During influenza epidemics a level of 33% has been reached. This means that one third of the deaths classified as chronic rheumatic heart disease was associated with influenza. During the minor epidemics this is about 5% with respect to age groups.
The influenza related mortality in chronic rheumatic heart disease mortality is the largest in people between 60 and 69 years, the smallest in people over 80 years. This is illustrated in figure 16 where the influenza related mortality of chronic rheumatic heart disease is set at 100.

figure 14 Observed and predicted mortality from chronic rheumatic heart disease in the total population. Black line: observed, red line: predicted.

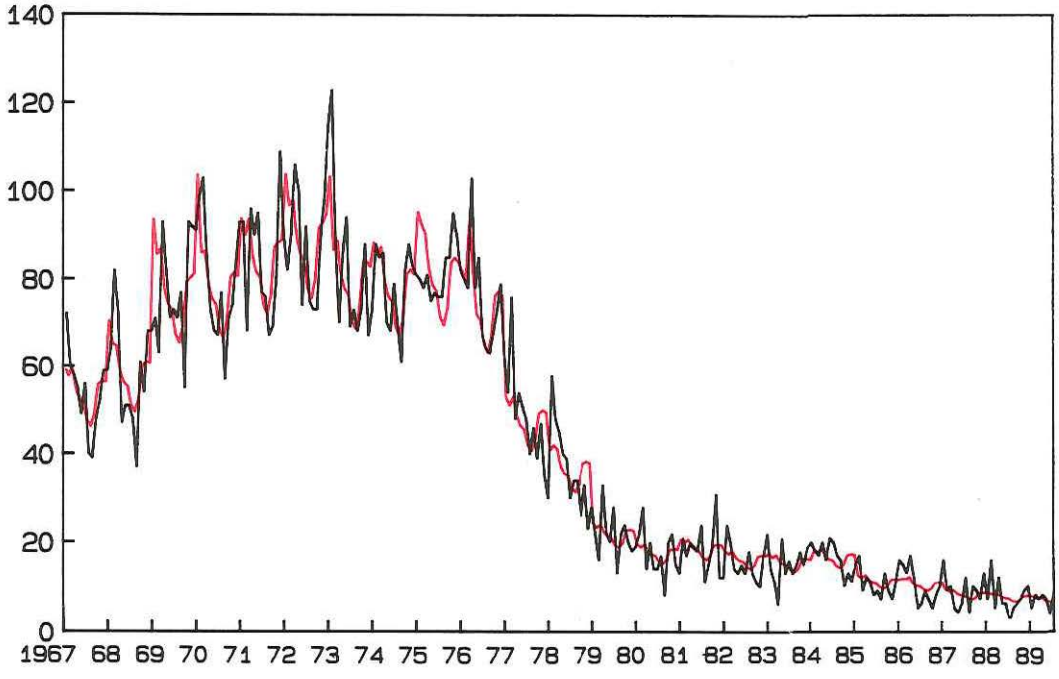


figure 15 Percentage of chronic rheumatic heart disease estimated in the model as being associated with influenza, per month

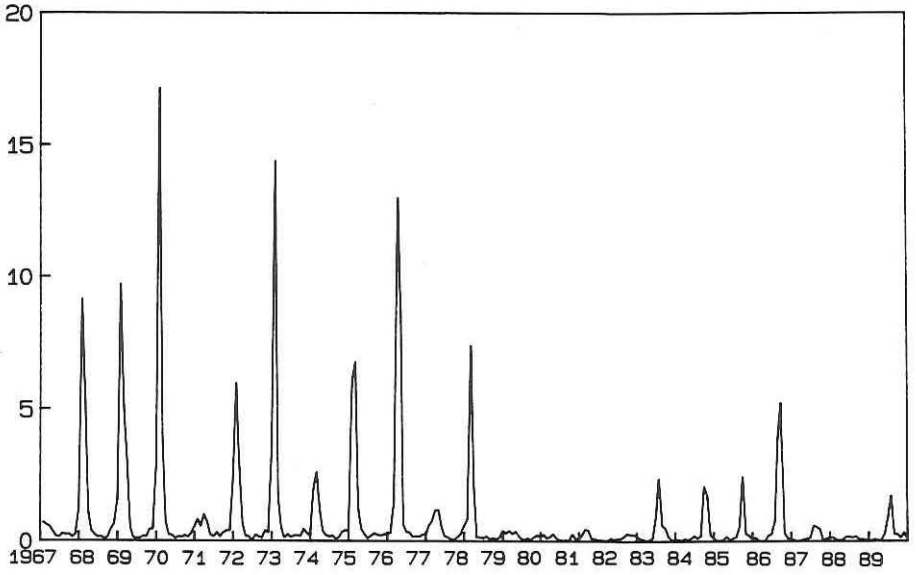
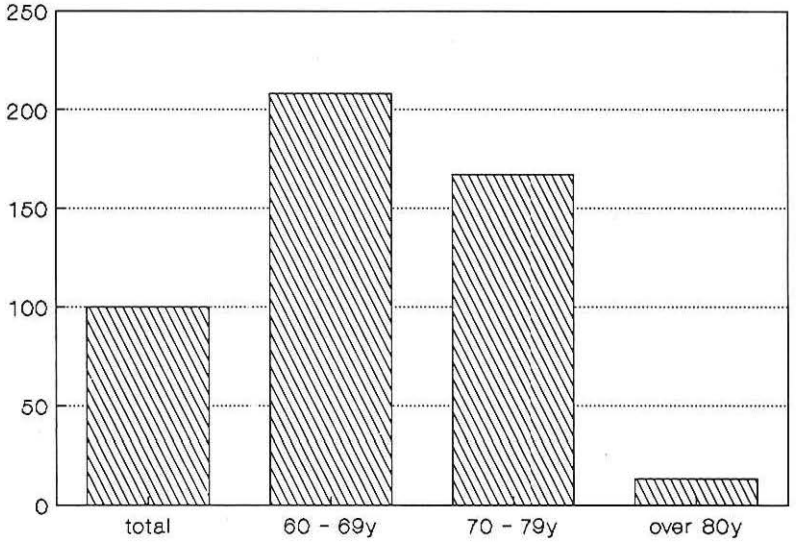


figure 16 Index of influenza related mortality of chronic rheumatic heart disease by age group.



Hypertensive disease (essential benign/malignant hypertension etc).
Figure 17 represents the observed and predicted total mortality registered as hypertensive disease. The incidence shows a decreasing trend until 1981, after 1981 the incidence increases. The incidence is between 50 and 100 death cases per month in The Netherlands. Figure 18 shows that the proportion of deaths registered as hypertensive disease associated with influenza can reach the maximum of 33 per cent (1969/70). During the mild epidemics this fraction is between 5 and 10 per cent.
The largest fraction hypertensive heart disease related to influenza is in people over 80 years, the smallest in people between 60 and 69 years (see fig. 19).

figure 17 Observed and predicted mortality from hypertensive disease in the total population. Black line: observed, red line: predicted.

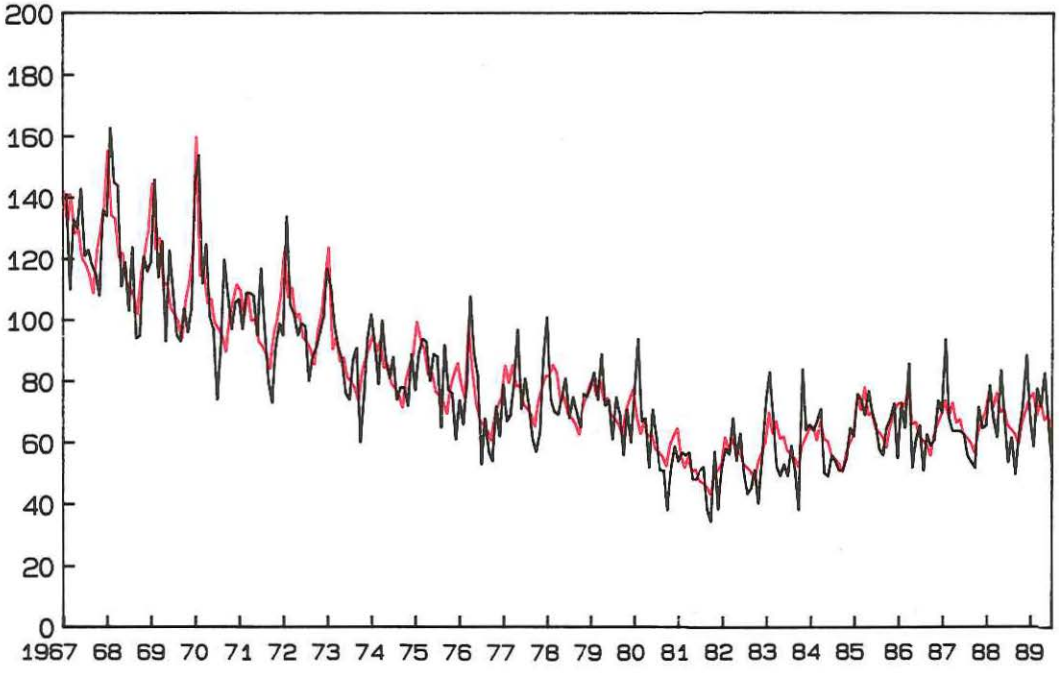


figure 18 Percentage of hypertensive disease estimated in the model as being associated with influenza, per month

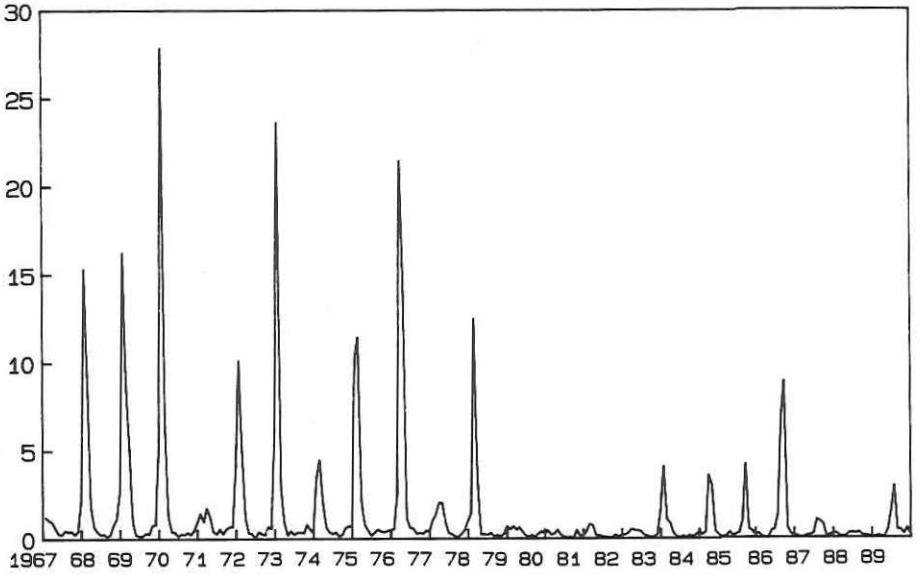
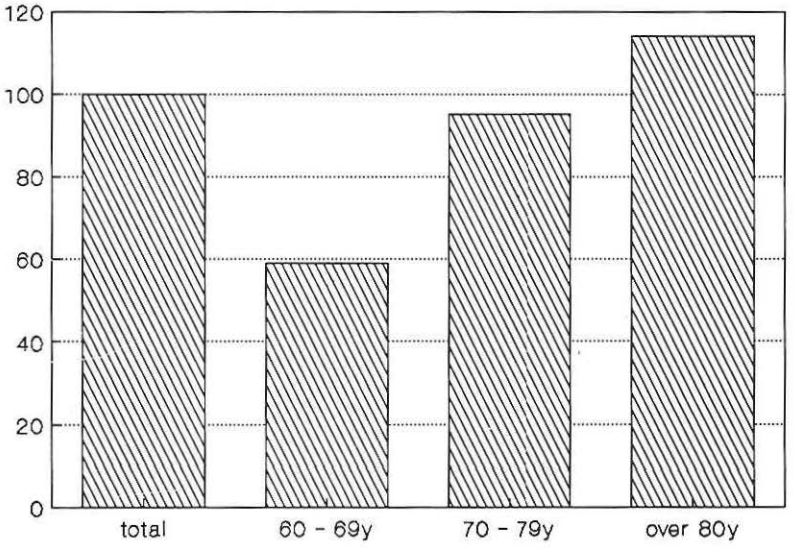


figure 19 Index of influenza related mortality of hypertensive disease by age group.



Ischemic Heart Disease (myocardial infarction, (sub)acute forms of ischemic heart disease etc).
As can be seen in figure 20 the incidence of ischemic heart disease mortality is much larger than for the two death causes mentioned before. The incidence is between 1500 and 2500 per month in The Netherlands. The model does fit the observed mortality quite well. In this diagnostic subgroup the fraction of influenza related ischemic heart disease deaths is about 22% at its maximum, somewhat less than in the earlier two subgroups. During the mild epidemics the fraction is between 3 and 8 per cent (see figure 21).
The largest fraction is in people over 80 years, the smallest in people between 60 and 69 years see figure 22).

figure 20 Observed and predicted mortality from ischemic heart disease in the total population. Black line: observed, red line: predicted.

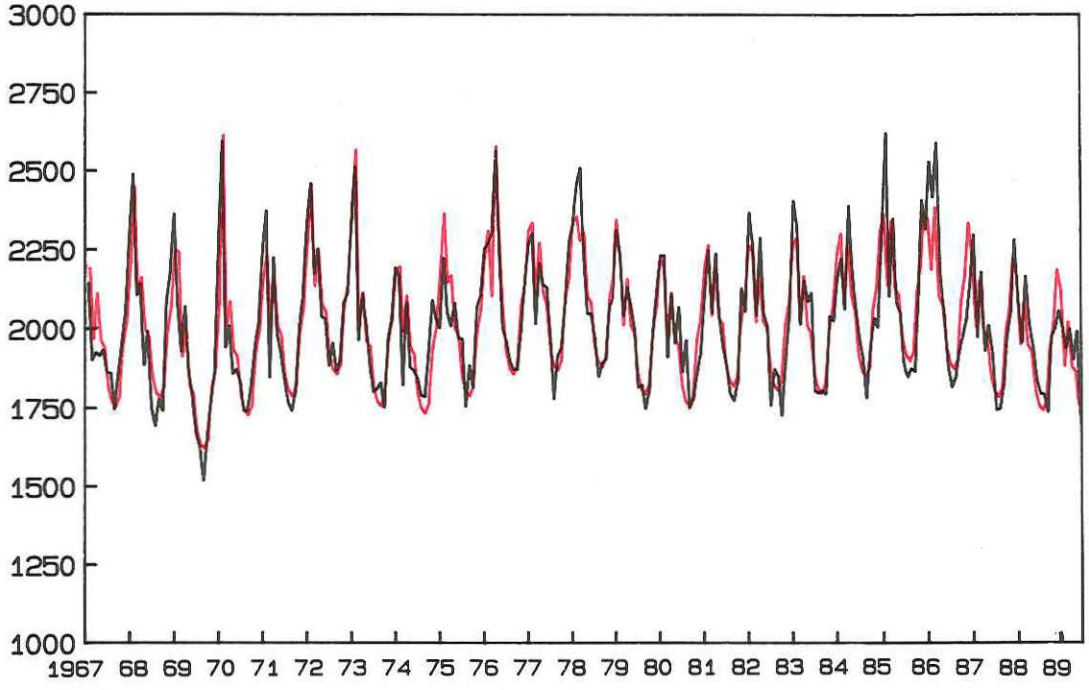


figure 21 Percentage of ischemic heart disease estimated in the model as being associated with influenza, per month

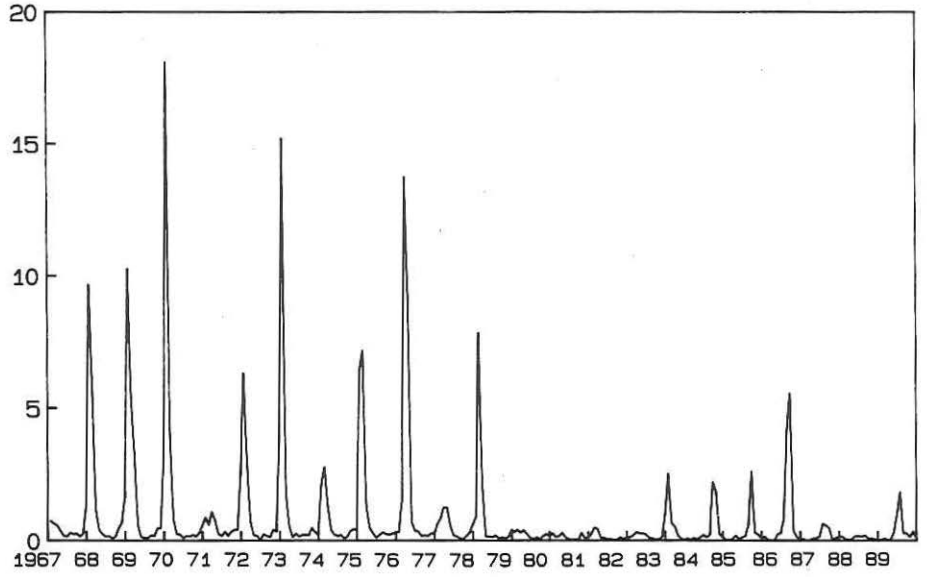
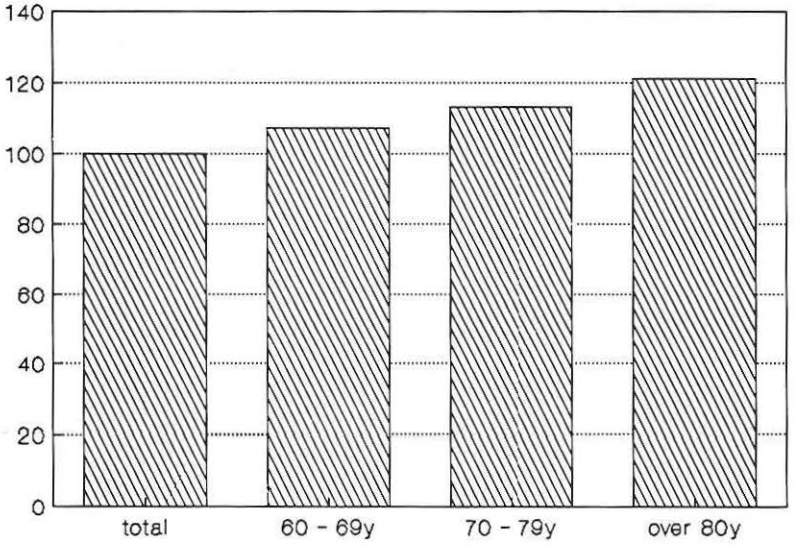


figure 22 Index of influenza related mortality of ischemic heart disease by age group.



Other forms of Heart disease (endocarditis, pericarditis, myocarditis, arteriosclerosis, dysrhythmias, conduction disorders etc).
It is clear that every version of ICD classification comprises a variety of diseases, each with its own incidence (figure 23). The differences between the versions will not invalidate the model because it takes account of year effects, so the differences due to the versions are accounted for. The model seems to fit fairly well. Figure 24 represents the proportion of influenza related mortality in this subgroup. In the age-group 70-79 the maximum level of this proportion is 36%. During the mild epidemics the average proportion is between 8 and 15 per cent. In the age group 60 - 69 this proportion is the smallest (see figure 25).

figure 23 Observed and predicted mortality from other forms of heart disease in the total population. Black line: observed, red line: predicted.

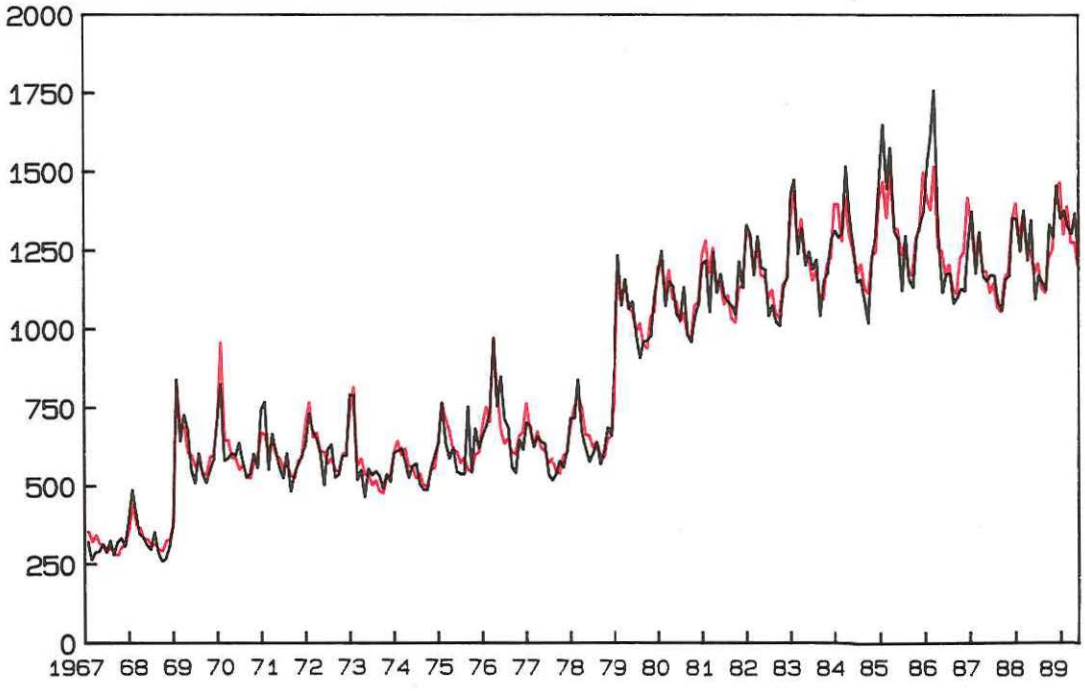


figure 24 Percentage of other forms of heart disease estimated in the model as being associated with influenza, per month

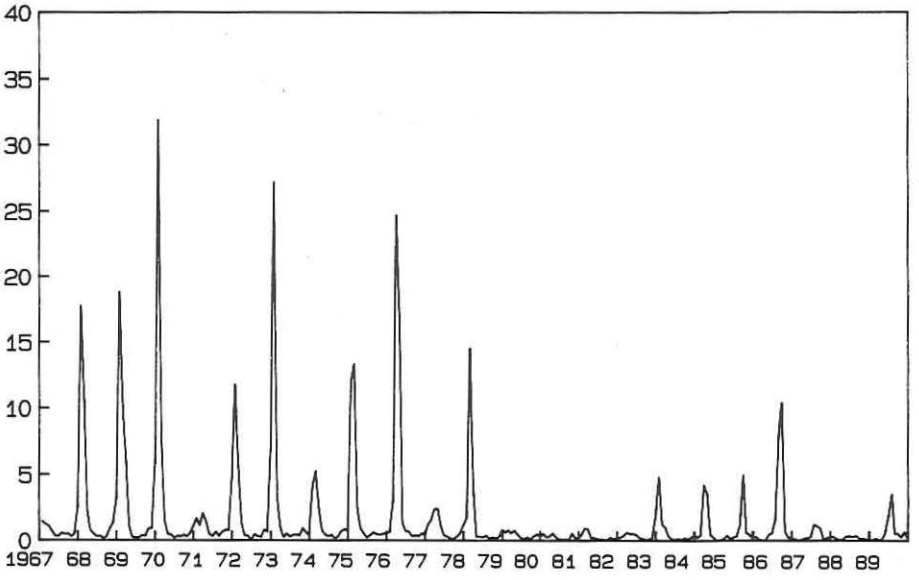
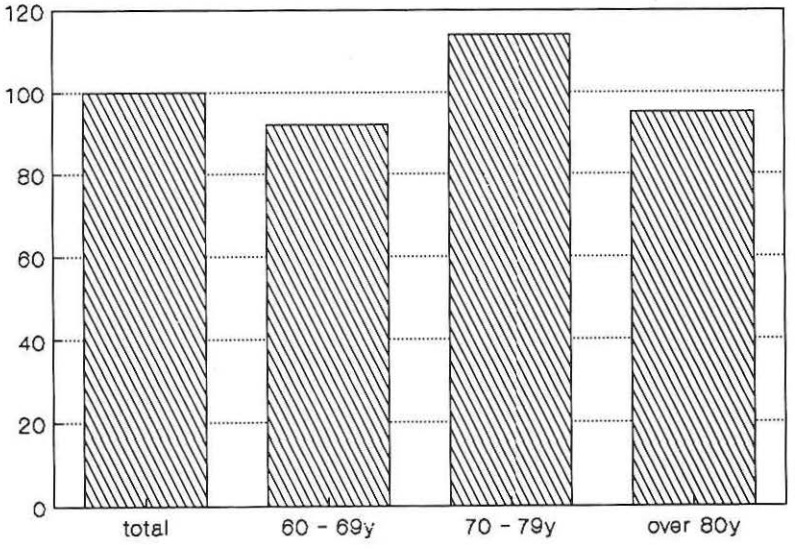


figure 25 Index of influenza related mortality of other forms of heart disease by age group.



Cerebrovascular disease (subarachnoid hemorrhage, cerebral hemorrhage, occlusion, transient cerebral ischemia etc).
Figure 26 represents the observed and the predicted mortality. The incidence is between 900 and 1400 deaths per month. Any classification ruptures are not manifest in this figure.
From figure 27 it can be seen that the maximum proportion of influenza related mortality in cerebrovascular diseases is about 23 per cent. During mild epidemics the average is between 4 and 8 per cent. The percentage of influenza related mortality is most obvious in the age-group over 80 years. In people between 70 - 79 this proportion is smaller (see fig 28).

figure 26 Observed and predicted mortality from cerebrovascular disease in the total population. Black line: observed, red line: predicted.

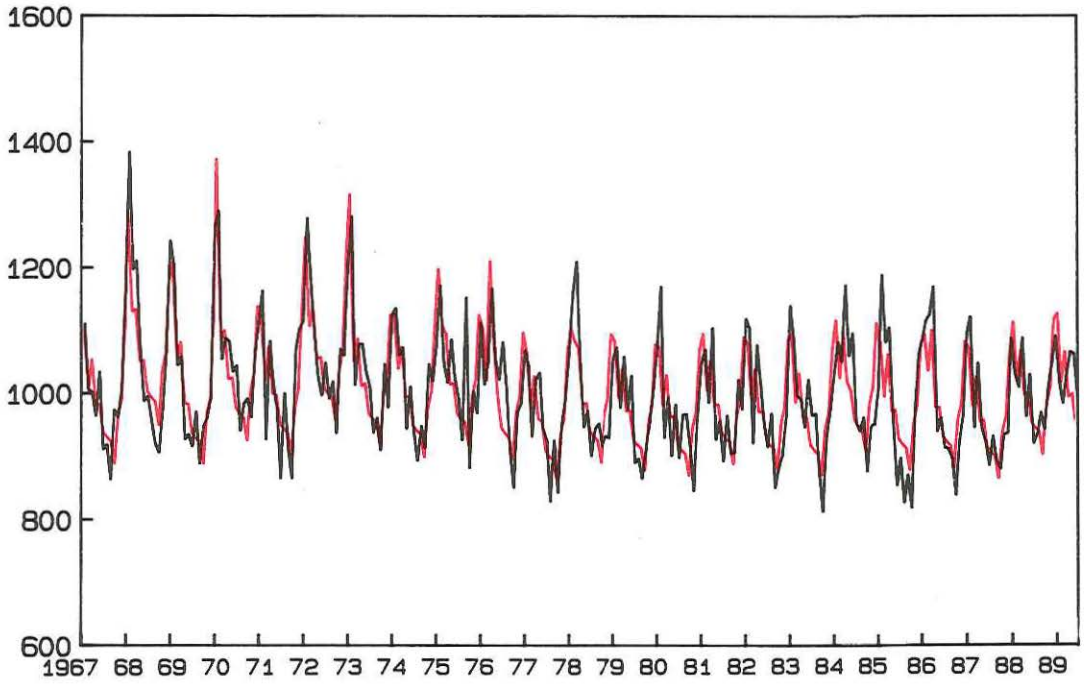


figure 27 Percentage of cerebrovascular disease estimated in the model as being associated with influenza, per month

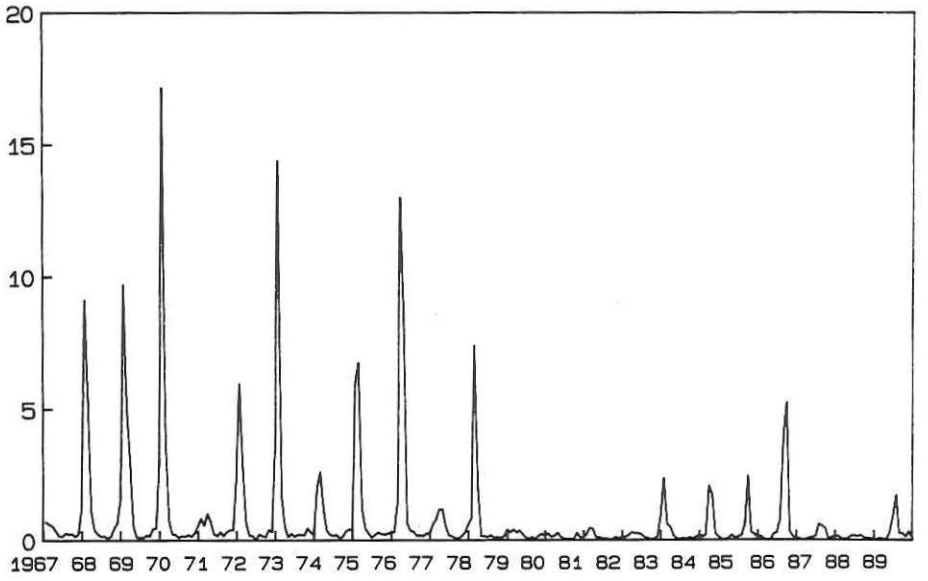
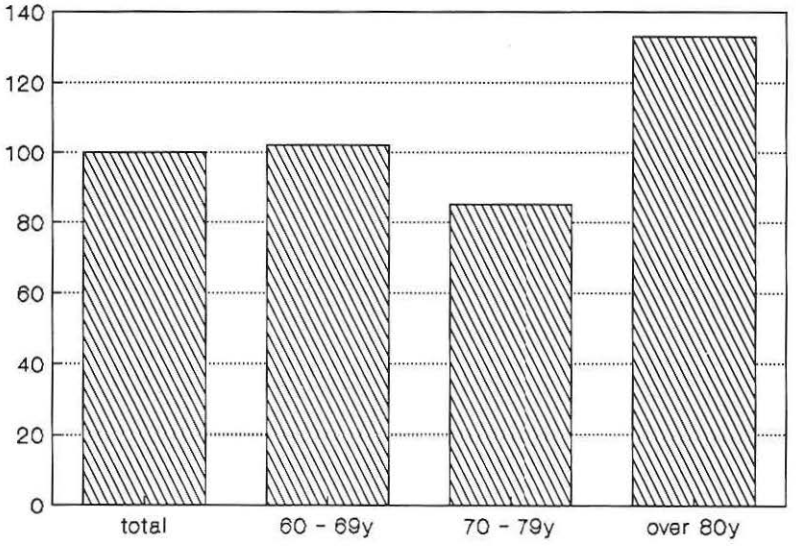


figure 28 Index of influenza related mortality of cerebro- vascular disease by age group.



The influenza related mortality in the diagnostic group lung diseases when subdivided according to two death causes is considered below.

Pneumonia (lobular, broncho, pneumococcal pneumonia etc)
The observed and predicted mortality respectively are presented in figure 29. The variation between the seasons regarding incidence are greater in this subgroup than was found in the heart disease group. The incidence is between 200 and 400 deaths per month. Any classification ruptures are not manifest.
Figure 30 shows the proportion of influenza related deaths within the pneumonia subgroup. The maximum level of this proportion is 68%, this means that during a severe epidemic more than 50% of mortality in this subgroup is associated with influenza. During mild epidemics this may reach a level between 15 and 25%. The proportion influenza related mortality is largest in the age group 70 - 79 year and smallest in age group over 80 years (see fig 31).

figure 29 Observed and predicted mortality from pneumonia in the total population. Black line: observed, red line: predicted.

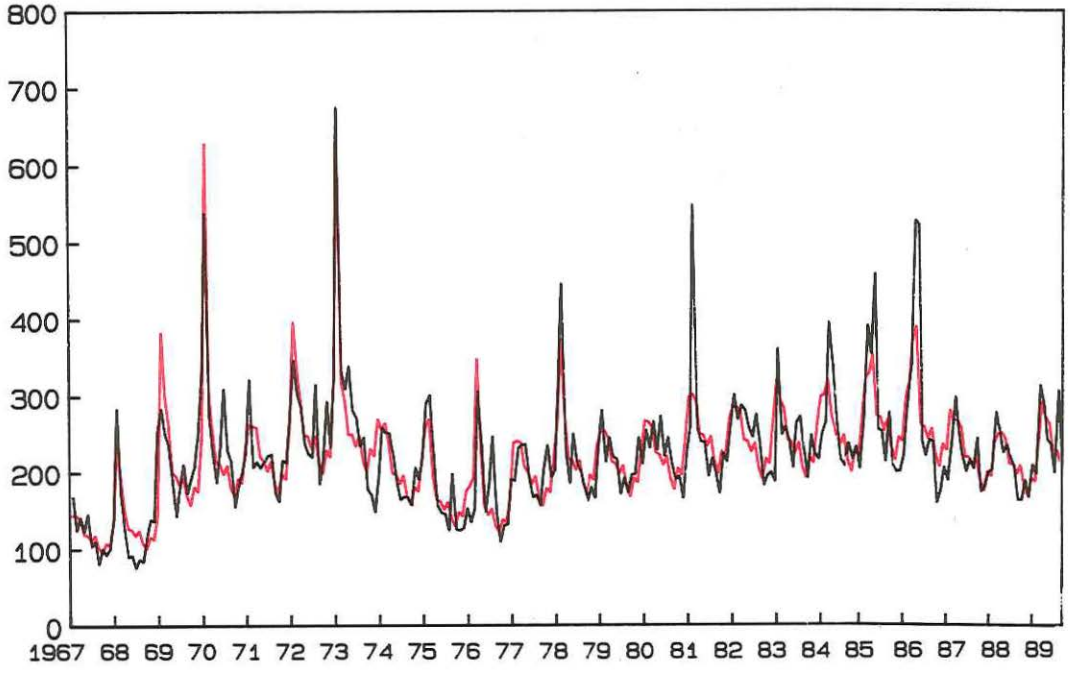


figure 30 Percentage of pneumonia estimated in the model as being associated with influenza, per month

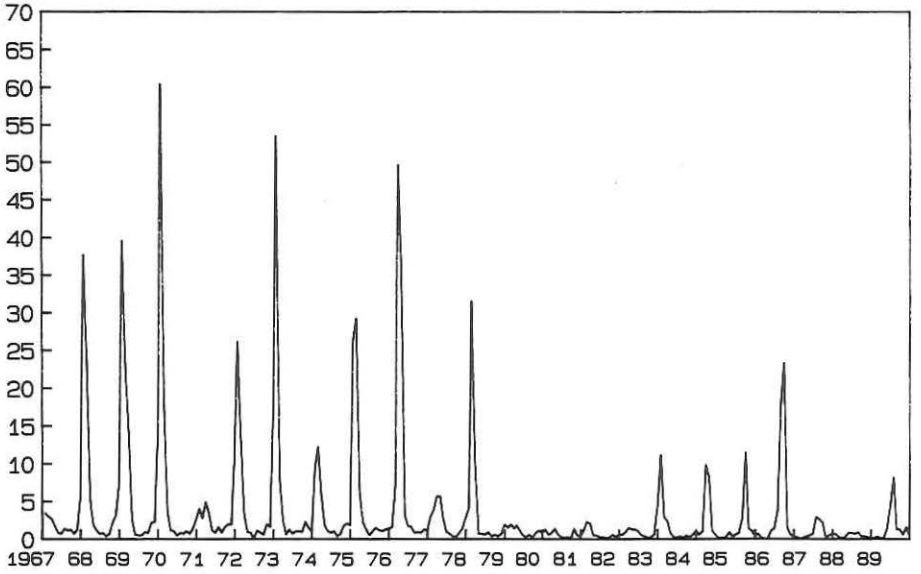
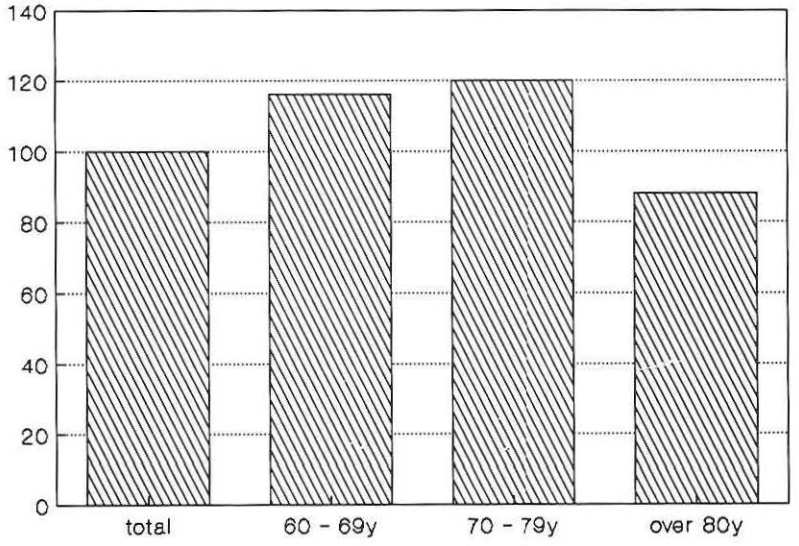


figure 31 Index of influenza related mortality of pneumonia by age group.



Bronchitis, emphysema and asthma (bronchitis, bronchiolitis etc)
Figure 32 shows the predicted and observed mortality respectively of bronchitis, emphysema and asthma. The incidence is between 200 and 400 per month in The Netherlands.
Figure 33 shows the proportion of influenza related mortality in the subgroup. The maximum proportion is about 56%. During mild epidemics this level is between 10 and 20%. In the age group 60 - 69 this proportion is the largest, in age group over 80 year the smallest (see fig 34).

figure 32 Observed and predicted mortality from bronchitis, emphysema and asthma in the total population. Black line: observed, red line: predicted.

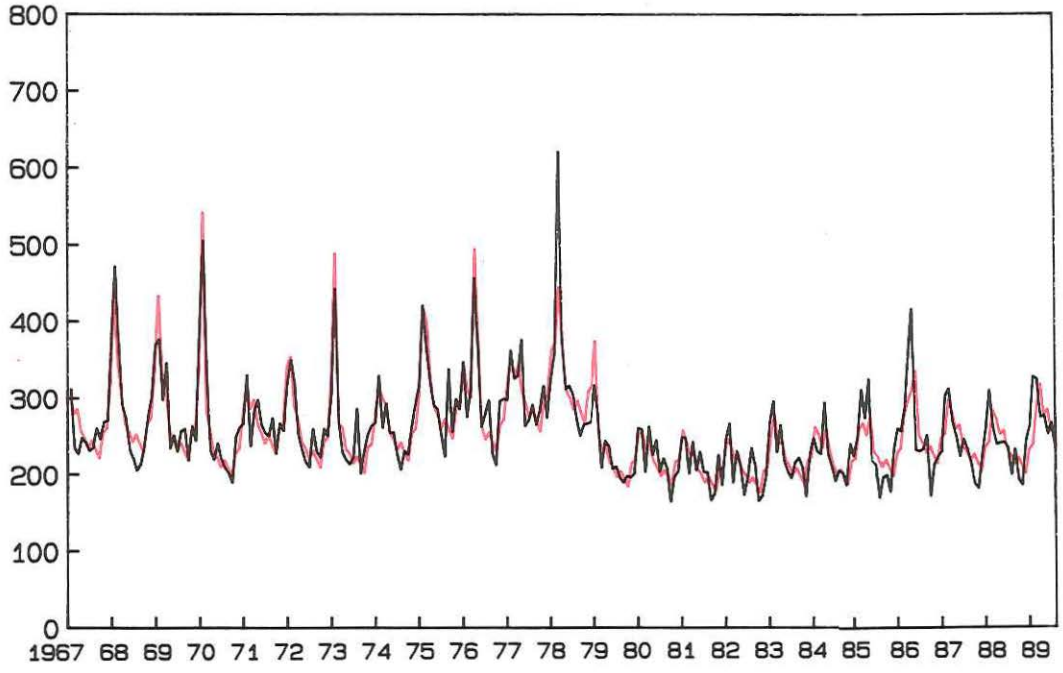


figure 33 Percentage of bronchitis, emphysema and asthma estimated in the model as being associated with influenza, per month

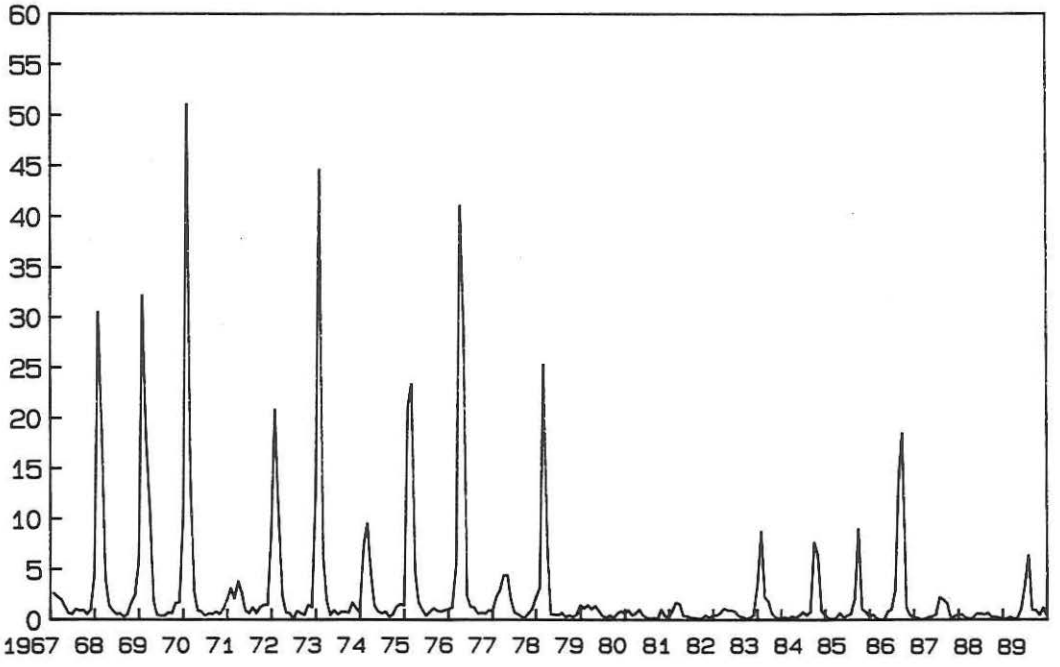
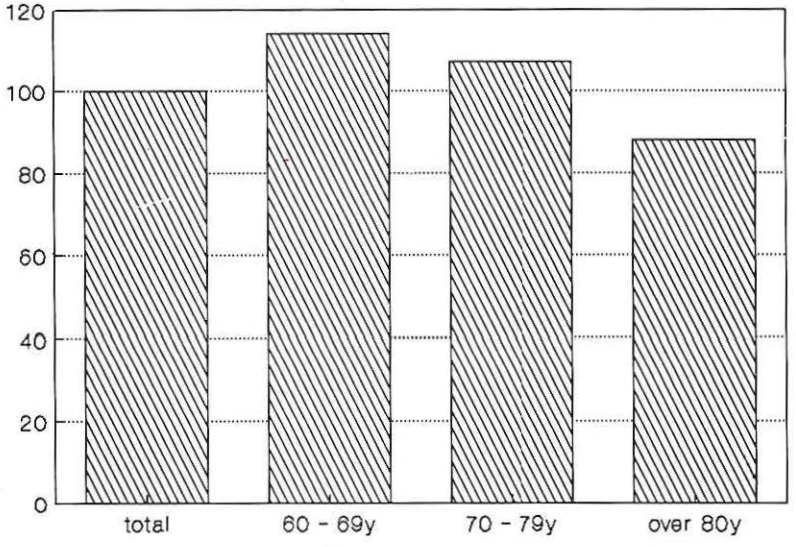


figure 34 Index of influenza related mortality of bronchitis, emphysema and asthma by age group.



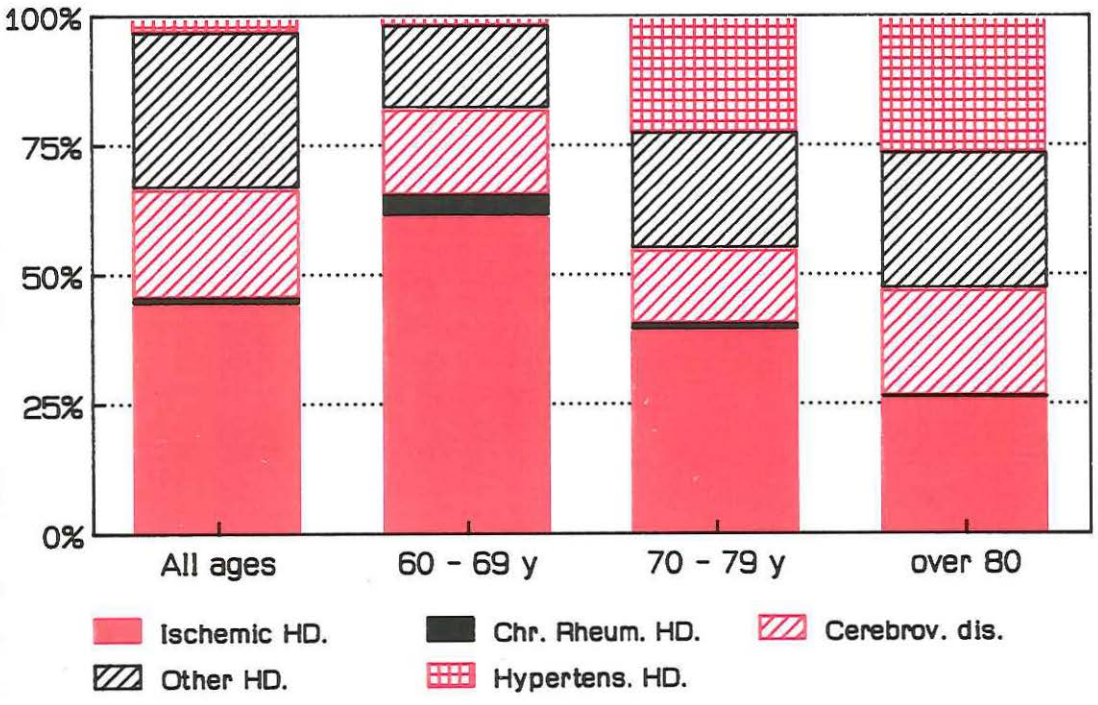
In section 5 every death cause was reviewed separately with respect to influenza related mortality. In this section the influenza related mortality for various subgroups will be compared within each diagnostic category. With respect to heart disease two questions are important to answer.

First how does the influenza related mortality vary between the five different death causes of heart disease and second how does influenza related mortality change within each death cause group.

The first question is answered in figure 35. For all ages taken together about 44% of the influenza related mortality in heart disease is found in the subgroup ischemic heart disease (myocardial infarction), 1% in the subgroup chronic rheumatic heart disease, 3% in the subgroup hypertensive heart disease, 30% in the subgroup "other heart disease" and 21% in the cerebrovascular disease.

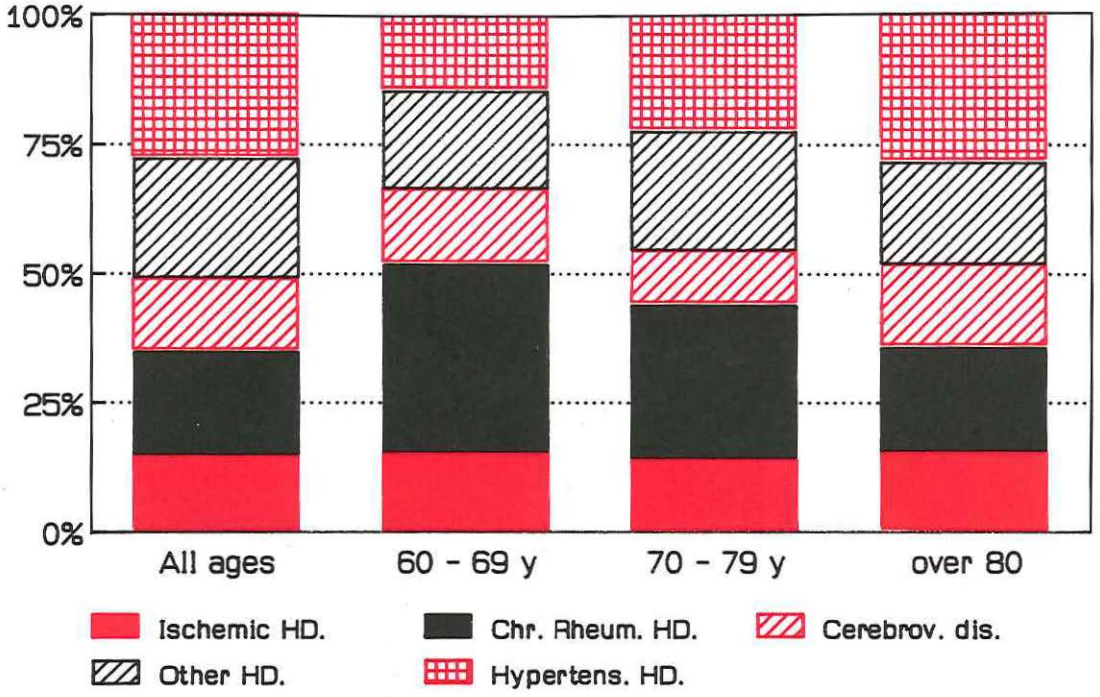
Considering age groups separately the largest proportion of influenza related mortality is diagnosed as ischemic heart disease (61%) in the age-group 60-69. In the age-group 70-79 this proportion is 49% and in the age group over 80 years it is 34%.

figure 35 Influenza related heart mortality by death cause per age group



The second question is considered in figure 36. Differences between death causes apparently are small as are differences between the age groups. At first glance influenza related mortality seems largest in chronic rheumatic heart disease; however the number of deaths in this subgroup is small, which makes the regression model less reliable.

figure 36 Proportion of Influenza related heart mortality within each death cause by age group



Next we will consider the two analogous questions with regard to both death causes under lung disease. The first question is answered in figure 37 and 38. For all ages taken together there is a fifty-fifty distribution with respect to influenza related mortality between the two death causes. Considering age groups separately in the age-group 60-69, the influenza related mortality is 25% in subgroup pneumonia. This proportion is increased in age group over 80 years to 70%.
The proportion of influenza related deaths in the subgroup of pneumonia is the same as in the subgroup of bronchitis.

figure 37 Influenza related lung mortality by death cause per age group

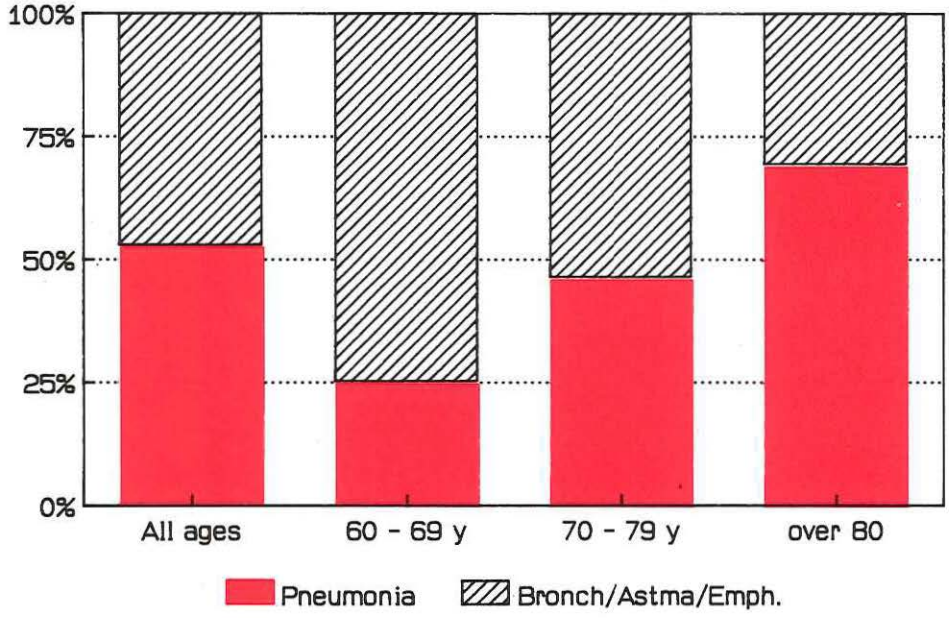
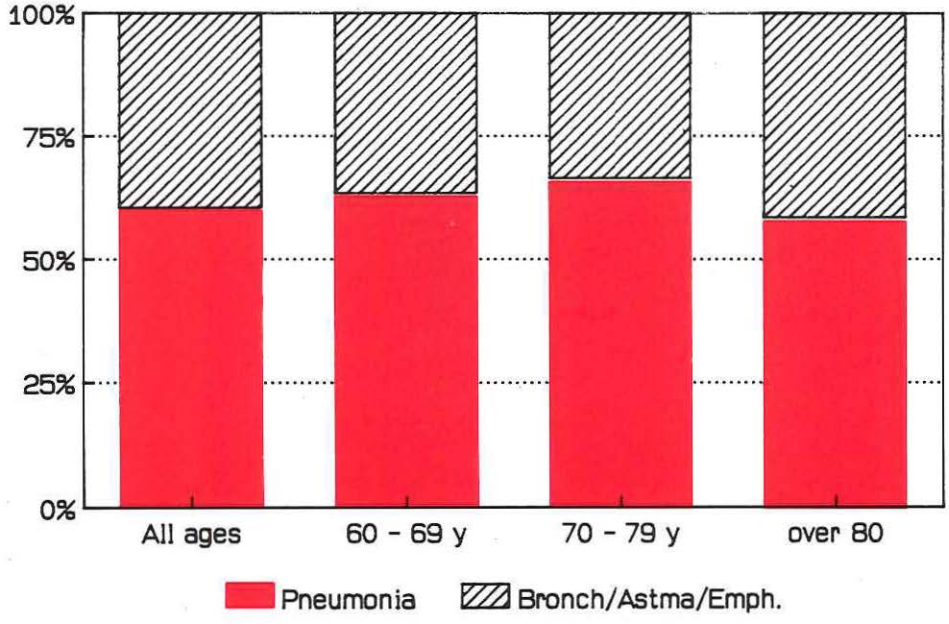


figure 38 Proportion of Influenza related lung mortality within each death cause by age group



Virological Results

Concerning the merits of the regression model applied in this study, the following observations can be made.

In the seasons-years 1970-71, 1971-72 and 1972-73 the total mortality was correctly predicted by the model. In the season 1972-73 the mortality was high, presumably because of the new drift virus A/England(H3N2) which appeared after the 4 year A/Hong Kong(H3N2) period[6].

In 1973-74 actual mortality was less than predicted by the model. In the U.K. the A/England(H3N2) strain was replaced by A/Port Chalmers(H3N2). The pattern of influenza infection was rather unusual in this epidemic. Both influenza A and B were circulating and the influenza A epidemic had a very prolonged course [7]. In The Netherlands the most frequently isolated strain was B/England and caused less mortality than predicted by the model. An explanation could be that the influenza B causes a lot of mild influenza-illnesses but relatively less mortality in this season.

It is remarkable that the wave of A/Port Chalmers cause high mortality in 1974-75 but was predicted by the model.

In 1975-76 the A/Victoria(H3N2) arrived and caused high mortality, much higher than predicted by the model. The A/Victoria(H3N2) showed considerable drift from the A/Port Chalmers(H3N2). The effect was that the virus could spread throughout the country.

The next year (1976-77) the same virus circulated but caused less mortality due to the immune status from the year before.

The A H1N1 that circulated in the world from 1947 to 1957[8] reappeared in 1977-78. In general, the excess mortality is known to occur mostly in the elderly. But older people (>29 years old) had already antibodies to this strain[9] [10] and the virus was isolated particularly in young people. This could be a reason that this strain caused less mortality than predicted[11] [12] by our model. In the next years the influenza epidemics are less striking except in the last epidemic 1988-89. This epidemic caused in The Netherlands more mortality than predicted. The reason might be that two A strains (H1N1 and H3N2) and the B virus were epidemic[13].

Conclusions & Discussion

In this study the excess mortality due to influenza has been estimated using a regression model based on four parameters: influenza-activity, month, year and population.
The influenza-activity parameter which gave the best fit of the model is the influenza-mortality per month in the total population. No clear time-lag effect has been found which is taken as an indication that the major effect of influenza-activity on mortality for other causes does occur in the same month.

Our overall analysis indicated that one registered influenza death case is related with an overall 2.6 other death cases. This influenza related mortality occurs for 50% in the age group 60 - 79 and for the age group over 80 years 45% and only 5% in the age group under 60.

Almost half of the influenza related mortality is estimated to occur in the diagnostic group of heart diseases, about 25% in the group of lung diseases and about 30% in the remaining group of other mortality (not further defined).
In each diagnostic category (heart, lung and other) the age distribution is about the same with about 95% of the death cases in age group over 60 year.

Concerning the influenza related mortality in heart diseases the largest proportion occurs in the subgroup ischemic heart disease, next, other heart diseases and third, cerebrovascular diseases whereas hypertensive heart disease and chronic rheumatic heart disease rank fourth and fifth.
The proportion of influenza related mortality within subgroups by death cause is substantially the same. So the influenza related mortality is for example not associated with one particular heart disease.

In the category of lung diseases the distribution of influenza related mortality in the subgroups by death cause, pneumonia and bronchitis/emphysema/asthma is fifty-fifty, when all ages are considered together. But the proportion of influenza related lung deaths is smallest in the pneumonia subgroup in age group 60 - 69 and larger over 80 years i.e. about 70%. Within the two death cause subgroups the percentage influenza related mortality is the same in the various age groups.

During severe epidemic the proportion of influenza related mortality did reach a maximum level of 25%.

In the studied period (22.5 years) the average yearly direct mortality and related mortality for influenza turned out to be more than 2000 in people over 60 years in The Netherlands.

An extreme high value of the scaled deviance, i.e. in the upper 5% tail of its chi-square distribution, warrants the conclusion that the model does not fit well enough. There is overdispersion (or extra-Poisson variation) in the data, probably due to unobserved heterogeneity caused by (unknown or unobserved) explanatory variables not incorporated into the model. Since the scaled deviance is proportional to the underlying monthly number of mortality cases and the population sizes, scaled deviance scores can become extremely high if there are model violations in a situation with very large numbers of observations per design point, as is the case here in some analyses.

Already in 1847 Willaim Farr, founder of modern concepts of surveillance[14], developed the notion of excess mortality. Farr ascribed the total excess mortality from all causes to the occurrence of an influenza epidemic. He proposed a method that started from the calculated expectancy or "mortality for the season".
For the population of London between 28 November 1847 and 1 January 1848 he calculated the excess mortality for all causes to be: 5067, including influenza mortality (1131) and mortality from bronchitis/pneumonia and asthma (2054). The resemblance with our approach is remarkable. Farr established that about 45% of the total mortality during the influenza epidemic was related to influenza. In our study we estimated the maximum level to be 26% which was reached in 1969-1970. The difference may be due to various factors including refinements in our model, which takes into account the long term effect and season effects in a period of 22.5 years. The proportion of influenza-related mortality within the group of lung diseases was given as 71% by Farr, whereas we found 62% with our model. For one influenza death registered according to Farr another 3.5 deaths were associated with influenza, whereas our model estimated that as 2.6. These differences may be due to a great many factors including the epidemic-features and improved sanitary conditions. Also the availability of antibiotics did decrease the impact of influenza.

Some time after Farr, Frost[15] and Pearl[16] appear to have been the first to utilize the concept of excess mortality to study influenza epidemics in the United States. Pearl showed that pre-existing ailments of the lungs, heart and kidneys were directly associated with increased mortality during influenza epidemics.

In 1930 Collins[17] proposed a method to estimate the baseline expected mortality from consideration of the weekly number of deaths recorded in years without major epidemics. He used moving averages to prepare figures of the expected mortality according to season. Collins also used his results to characterize both the extent of epidemics regionally and their movement across the United States[18].

Serfling extended the method of Collins and used mathematical functions. In 1963 Serfling[19] [20]recommended separate estimation of secular (long-term) trend and seasonal change. In parentheses, Farr did not make any correction for a secular trend.

Serfling wrote "although excess pneumonia-influenza mortality lags about 4 weeks behind increases in influenza morbidity, it serves as the primary quantitative surveillance index". We did not recognize a time-lag of this order, using influenza mortality instead of morbidity as indicator. The primary target of Serfling was to discover an early signal of an influenza epidemic.
To achieve this he fitted a least squares straight line to weekly morbidity rates, for example, at week 40 of calendar years 1954, 1955 and 1956 and extrapolated this line to week 40 of 1957. At a distance of 1.64 standard deviations above this trend line he drew a line defined as the epidemic threshold line.

Housworth and Langmuir[21] reviewed excess deaths from respiratory causes in the United States and in England and Wales for the period 1957-1966. They suggested that excess deaths from all respiratory causes, and not of pneumonia and influenza alone, was the most suitable index for global comparisons of the severity of influenza epidemics.
Table 6 presents the percentages of influenza related mortality in three death categories, i.e. (I) respiratory diseases, (II) heart, circulatory, nervous diseases and (III) all other diseases (see table 6) In addition the distribution of excess mortality given by major cause of death according to both Housworth and Sprenger. It is not possible to compare directly the intensity rates of Housworth (i.e. proportion of influenza related mortality in a death cause group) to this study because Housworth chose different lengths for the whole epidemic period whereas in this study the rates are strictly based on calendar months.
The distribution of excess mortality by three major death causes is seen to be about the same in the two studies (see table 7).

Table 6 Percentage of influenza related mortality according to specific cause of death in this study (relative intensity) and distribution of excess mortality by major cause of death according to Housworth (1969) and Sprenger (1990).

death cause	proportion influenza related mort.	estimated excess mort. Housworth	Sprenger
I respiratory	38%	30%	34% 1)
II heart	7%	55%	45%
III other	3%	15%	22%
total	14%	100%	100%

1)according to figure 11: lung + influenza deaths / total= (5781+9710)/34810=0.34

In table 7 the estimated numbers of influenza related death cases per million inhabitants according to specific cause of death are presented. The agreement is remarkable. The overall figure of influenza related mortality is somewhat different (142 vs 162) but this can be due to the intensive epidemic period contained only in the study of Housworth (Asian flu period).

Table: 7 Estimated number of influenza related death cases per million inhabitants in specific cause of death group, according to Housworth and Sprenger, respectively.

death cause	Housworth	Sprenger
I respiratory	50	48 1)
II heart8	88	64
III other	23	31
total	162	142

1) estimated number of direct influenza & influenza related death cases is 2100 per year per 14.9 million inhabitants (see table 5), This is equivalent to 142 per million of which 34% for respiratory diseases that is 142 x 0.34 = 48 per million

Housworth and Langmuir also presented excess and expected rates for selected disease classifications. Arteriosclerotic heart disease was the only sub-classification examined other than pneumonia and influenza which showed significant excess during all periods. Their conclusion is in agreement with ours: "study of excess mortality by broad groups of causes revealed that deaths associated with respiratory diseases constituted consistently less than 50 per cent of the total excess. The actual proportion varied from 30 to 38 per cent in the more severe epidemics to less than 25 per cent in the milder epidemics. Excess deaths ascribed to diseases of the heart and of the circulatory and nervous system exceeded 50 per cent in all epidemics. Examination of excess mortality by certain specific causes showed that severe influenza epidemics influence mortality from tuberculosis, asthma, chronic rheumatic heart disease, and diabetic to a small but statistically significant degree". The only point to make is that in our study no distinguish was made for diabetics.

Rogot[22] studied the daily variation in USA mortality in the period 1962-1966. The most significant factors affecting mortality in the 5 years studied appeared to be the influenza epidemic in 1963 and the unusually hot weather occurring in mid-1966. They also saw a high correlation between influenza and coronary heart disease ($r=0.81$) and stroke ($r=0.75$), respectively. For total mortality they observed also a high relation ($r=0.87$), but contrary to our study they did not exclude influenza from the total mortality, so their independent variable (influenza-mortality) is included in their dependent variable (total mortality), which will inflate any correlation.

Clifford et al.[23] studied the monthly number of deaths from influenza in England and Wales during the period, October-April, for the years 1967-75. They estimated the recurring seasonal pattern in mortality by averaging the numbers in corresponding months for each of the 9 years.
Linear (or quadratic) regression functions were used to estimate long-term trends. The resulting estimates were multiplied by arbitrary constants and then added together to form a regression function. This function was then used to describe the seasonal pattern combined with a secular trend. In their study a great many independent variables were involved in the model. These included as influenza-activity measure the four-weekly incidence rate of influenza as diagnosed by the "spotter" practices provided by the Royal College of General Practitioners (RCGP) and in addition laboratory diagnosed virus infections, air temperature (lowest daily mean air temperature), number of years since a change in the influenza virus haemagglutinin antigen, serological immunity (proportion of the population with antibody to the prevailing strain). Contrary to our study their regression model is not based on the assumption that death cases are generated by a Poisson process. Their estimates of excess morbidity and mortality provide evidence that influenza often had a serious impact on the population, according to Clifford. In the larger epidemics as many as 25,000 people are estimated to have died in England and Wales for influenza and influenza related mortality which is equivalent to 520 per million. This number differs appreciably from our study where the maximum number of influenza and influenza related deaths was 345[2] per million inhabitants of all ages, in the season-year 1969-1970. According to our model the total impact of influenza in England and Wales with 45 million inhabitants would be about 15,500 (345 x 45), which is almost 40 per cent less.

Clifford stated that excess mortality in those aged 65 years and over represented about 65 per cent of the total excess mortality. In our study people over 60 represent 90 per cent of the total excess mortality.
In all the models investigated by Clifford the Royal College of General Practitioners (RCGP) consultation rate was found to be the most acceptable indicator of fluctuations in influenza incidence. The number of isolations of influenza A and B contributed little additional information; it was observed to be dependent of the amount of virological diagnostic work undertaken, the laboratory method used, and the current interest in influenza.

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[2] 95 observed influenza deaths and 250 estimated influenza deaths

Clifford had also anticipated that mortality might lag behind morbidity but this was not confirmed. Information about the antigenic drift also gave little additional information. The air temperature was found to be inversely correlated with the incidence of influenza and mortality. Because so many deaths occur among the elderly, it was considered that a large number of deaths in one winter might reduce the number of susceptibles likely to die in the next winter. However including a variable indicating death rate in the previous year into the model was not found to make a significant difference, according of Clifford. He calculated that there is an average of 1 in 750 people in the group of 65 years and over who died of influenza during the winter. In a large epidemic as in 1969/70 the proportion of this group who die may be 1 in 320. In our model the average of 701[3] people over 70 years and an average of 1238 in people over 60 years of age died of influenza or was associated with influenza.
The reason why Clifford estimates a greater impact of influenza compared to our study is not clear.

In 1980 Tillet, Smith and Clifford again presented a paper about the excess morbidity and mortality associated with influenza in England and Wales[24]. The model used in 1977 had been refitted to provide estimates of excess mortality for the period 1975-1978. For the season year 1975-76 they estimated 22,250 excess deaths in England and Wales of whom 88% were in the age group over 65 years. The majority of these deaths could be accounted for by respiratory causes (77%), according to Tillet. It is remarkable that their percentage excess deaths in the age group over 65 is now fairly in accordance with our study 90% of excess deaths in people over 60.
The proportion of respiratory diseases is still overestimated as compared to our study. In table 8 the main results in the study of Clifford and of Tillet et al. and our study are summarized.

[3] In the age groups 60-69y, 70-79, over 80, the average estimated related mortality and observed influenza are resp. 183 + 40 = 223, 584+ 167 = 751 and 1910 + 891 = 2801. With respect to the population size in a particular age group the average influenza and influenza related mortality can be calculated.

We also calculated a rank-correlation between the figures of Clifford (study 1977 and 1980) and our figures for 12 successive season-years. The rank-correlation is 0.89 including all of the years and 0.95 excluding the first year, which is fairly high. Clifford calculated for the first year (1967-1968) extremely high mortality, not according to our figures. Excluding this first year improves the rank-correlation and makes the results of studies comparable.

Table 8 Estimates of excess morbidity in England and Wales according to Clifford et al (1977) and Tillet et al (1980) and estimates of excess mortality per million inhabitants in The Netherlands according to Sprenger et al (1990). Rank numbers are given within brackets.

season-year	1980	1990
1967/68	26754 (1)	159 (5)
1968/69	12074 (6)	185 (4)
1969/70	25406 (2)	250 (1)
1970/71	2453 (12)	40 (11)
1971/72	16132 (5)	118 (7)
1972/73	16664 (4)	201 (3)
1973/74	7574 (8)	63 (9)
1974/75	7912 (7)	136 (6)
1975/76	17210 (3)	225 (2)
1976/77	5790 (10)	44 (10)
1977/78	6080 (9)	96 (8)
1978/79	5500 (11)	20 (12)

Alling, Blackwelder and Stuart-Harris[25] investigated the effect of influenza A on mortality in the United States by studying the monthly numbers of deaths during the years 1968-1976. The method of Clifford was used with some differences. The base line for mortality in the absence of an influenza epidemic was calculated from a regression equation based on the observed values of the indicator for influenza activity in 1970-1971. Information about air temperature, sickness benefits and infant mortality was not collected. The indicators of influenza activity used in their study were deaths from influenza and from acute respiratory diseases, in contrast to Clifford's indicator who employed morbidity.

Their estimated number of annual excess deaths averaged to 13,000 for total mortality, of which 9,500 in the age group 65 and over, 4500 in the group of cardiovascular causes, and 6800 in the group of acute respiratory causes. The proportion of excess mortality in people over 65 years is less than in our study (73% vs 90%), but the proportion of excess cardiovascular deaths (35 per cent) is in agreement with our study (34%). As can be seen in Table 9 the average excess mortality per million estimated by Alling is lower than in our study, and the distribution by epidemics is different. An explanation could be the different epidemic features between U.S.A. and Europe.

Table 9 Estimates of excess mortality per million population in United States according to Alling (1981) and estimates of excess mortality per million population in The Netherlands (1990). Rank numbers are given within brackets.

season-year	1981	1990
1968/69	235 (1)	185 (4)
1969/70	40 (5)	250 (1)
1970/71	67 (4)	40 (8)
1971/72	33 (7)	118 (6)
1972/73	114 (2)	201 (3)
1973/74	6 (8)	63 (7)
1974/75	6 (7)	136 (5)
1975/76	79 (3)	225 (2)
average	72	152

In 1980 Barker and Mullooly published a study on the impact of influenza in a defined adult population[26] [27]. They studied the occurrence of excess morbidity and mortality among subsets of the adult population in a prepaid group practice during two epidemics (1968-1969 and 1972-1973). The experience from 1970-1971, a nonepidemic year, was used as a reference for estimating excess rates. Their estimates of excess deaths per 100,000 population were 11 and 13 respective. In our study the respective numbers were 18.5 (1969-1970) and 20.1. Although the results in the study of Barker are comparable with ours, methodologically the study by Barker is weak since only one nonepidemic year (1970-71), was used as a reference for estimating excess rates.

Labelling a certain year, e.g., 1970-1971, as a "non-epidemic" year and using the number of deaths for that year as the baseline, above which deaths occurring in epidemic years, is a questionable practice. National surveillance reported in 1970-71 regional or widespread influenza activity in 12 of 30 states, compared to 18 states in 1969-1970, which was considered an "epidemic" year[28].
Therefore the year chosen, might be an unusual one, and in the study of Barker and Mullooly no allowance is made for secular trends in mortality or for other factors which can influence the number of deaths that occur during winter.

Choi and Tacker[29] [30] used the autoregressive integrated moving average (ARIMA) model of Box and Jenkins[31] to forecast weekly expected pneumonia and influenza (P&I) mortality figures, in weeks where there was no epidemic. Weeks in which there is an epidemic are replaced by these expected number forecasted by the ARIMA model. They define excess mortality as the difference between the observed P&I-mortality and the expected mortality. They use this excess mortality to define epidemics.
The ARIMA model is a model which uses the dynamics in the observed time series in order to be able to forecast. In the weekly figures dealt by Choi and Tacker it is plausible that there are such dynamics. In our figures, however which are monthly figures, we found only small (<0.25) serial correlations in the residuals, given our estimated model.

Glezen[32] suggested that pneumonia-influenza deaths (in his model the influenza-activity) represented a relatively small proportion of deaths that could be correlated with influenza during epidemics. About twice as many deaths attributed to ischemic heart disease occur during influenza epidemics and is related to pneumonia-influenza mortality. The fact that these deaths have been coded as ischemic heart disease may have resulted partially from the incomplete information supplied by physicians completing death certificates. It may also result from the fact that the rules for classifying deaths under the International Classification of Diseases, Adapted (ICDA) usually give precedence to the underlying condition even when pneumonia is listed as the immediate cause.

In 1983 Tillett et al[33] fitted a multiple regression model to estimate excess deaths by age group and certified cause of death in the studied period 1968/69 to 1977/78.
They estimated that on average 67% of excess deaths were certified as respiratory disease and 31% as circulatory system disease. Of the latter 40% were attributed to ischemic heart disease and 20% to cerebrovascular disease. This is comparable to our results: of the influenza related mortality in heart disease about 44 per cent is attributable to ischemic heart disease and 21 per cent to cerebrovascular disease.
About 82% of influenza related mortality were in the group of 65 years and over.
Unlike Alling et al, Tillett et al did not include summer periods because in their opinion this would increase the background noise and hence the standard errors of estimated excess mortality rates. In their regression models they also investigated whether winter influenza mortality induced a deficit of mortality in following summers. They could not demonstrate such serial correlation.

In 1987 Lui and Kendal[34] reported that about 80 to 90 per cent of all influenza-associated deaths were in persons over 64 years old and that the incidence of "influenza-associated" pneumonia and influenza deaths of US residents over 64 years old was from 34 to 104 times greater than that in persons under 65 years. They noted some limitation in the use of mortality data to quantify the impact of influenza epidemics, because after influenza activity has been publicly reported there may be an increased tendency to classify deaths as due to "pneumonia and influenza". This will amplify the rate of increase in pneumonia and influenza deaths or, when a decline in influenza activity has been reported, some bias toward a decrease in the classification of deaths related to "pneumonia and influenza" may result.

The studies discussed so far mainly considered influenza related mortality in general. We will now review some studies concerning influenza related heart disease.

Vikerfors et al[35] studied the occurrence rate of infectious agents in acute myocarditis. In a prospective study, 57 patients having a preliminary diagnosis were investigated. Using a routine serologic test battery covering influenza viruses A and B, adenovirus, Coxsackie virus group B, ECHO virus, Chlamydia psittaci, Mycoplasma pneumoniae and hemolytic streptococci group A, a probable etiology could be documented in 14 cases. They only found one influenza fourfold titer rise.

Montague et al[36] studied possible cardiac effects of common viral illnesses. They compared the clinical electrocardiographic and echocardiographic findings from 32 patients (mean age 26) during the acute and recuperative phases of viral illness, with similar data from a healthy age- and sex-matched normal control group. They reported three major findings. First, patients with common acute viral illnesses did not show; any cardiac symptoms; or abnormalities on cardiac clinical examination and had largely normal qualitative electrocardiographic patterns. Second, late repolarization integral values were observed much less than in the control group. Third, there were significant temporal increases in both systolic left ventricular performance and late repolarization values, concordant with clinical recovery from the acute illness. In conclusion, these findings suggest quantitatively subtle and clinically benign, cardiac effects of common viral infections.

Acute myocardial infarction is, in the majority of cases, caused by an occlusive thrombus in an atherosclerotic coronary artery[37]. Infections, especially viral infections, have been suggested to be involved in the development of acute myocardial infarction, but the evidence so far is controversial[38 39].
Mattila[40] investigated the association of viral infections with acute myocardial infarction in a case-control study involving 40 patients with an acute myocardial infarction, 41 random controls and 30 patients with chronic coronary disease. All individuals were males aged 50 years or less. No differences were observed between the groups as to the occurrence of antibodies against 16 viruses.

Bainton, Jones and Hole[41] examined the rate of deaths from ischaemic heart disease at the time of an influenza epidemic. In their opinion they had confirmed a temporal relationship between influenza-activity and increased death rate from ischaemic heart disease. Their findings were consistent with the hypothesis that influenza preceded infarction. On the other hand it is conceivable that case-fatality in myocardial infarction is increased during an influenza epidemic.
Engblom et al[42] reported a fatal influenza A myocarditis with isolation of virus from the myocardium. Histology of the myocardium revealed extensive lymphocytic infiltration and marked destruction of the myocardial cells. In most of the reported cases the evidence is only serological, and the virus has very rarely been isolated from the myocardium[43].

Timmons et al[44] tested the hypothesis that intracranial aneurysm develops because of viral infection that produces arterial damage, and that aneurysmal rupture is related to viral infection. Some viruses were studied among which influenza A and B, in 29 patients and 29 controls. They did not reveal positive correlations between the viral titers and aneurysmal subarachnoid hemorrhage.

In summary, no clear evidence has been published so far about a direct relation between influenza and heart-disease. Our study indicates that influenza related deaths only occur during an influenza epidemic. In all studies reviewed above it was tried to find a virological agent without particular reference to the influenza season. If there would indeed be a direct relationship between influenza viruses and heart-diseases, i.e. influenza virus causes heart deaths, the question is how this can be explained.

More research has to be done during an influenza epidemic to find the influenza virus or only a fragment of the RNA. Use of new methods of molecular biology may furnish ways to detect influenza virus in material of the tractus respiratorius.

It is likely that this analysis provided a conservative estimate of the potential full impact of influenza epidemics, because an appreciable proportion of the elderly and other high-risk persons received yearly influenza vaccine or at least prior to each of the epidemics included in the study. It is reasonable, therefore, to assume that thereby some excess deaths were in fact prevented.

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International Classification of Diseases

Chronic Rheumatic Heart Disease

ICD 7 Chronic Rheumatic Heart Disease B25 (410-416)

410 diseases of mitral valve
411 diseases of aortic valve, specified as rheumatic
412 diseases of tricuspidalic valve
413 diseases of pulmonic valve, specified as rheumatic
414 other endocarditis, specified as rheumatic
415 other myocarditis, specified as rheumatic
416 other heart disease, specified as rheumatic

ICD 8 Chronic Rheumatic Heart Disease B26 (393-398)

393 diseases of pericardium
394 diseases of mitral valve
395 diseases of aortic valve
397 diseases of other endocardial structures

ICD 9 Chronic Rheumatic Heart Disease AM26 (393-398)

393 chronic rheumatic pericarditis
394 diseases of mitral valve
395 diseases of aortic valve
396 diseases of mitral and aortic valves
397 diseases of other endocardial structures
398 other rheumatic heart disease

Hypertensive disease

ICD 7 Hypertensive Heart disease B27+B28 (440-447)

440 essential benign hypertensive heart disease
441 essential malignant hypertensive heart disease
442 hypertensive heart disease with arth. nephrosclerosis
443 other and not specified hypertensive heart disease
444 essential benignant hypertension
445 essential malignant hypertension
446 hypertensive with arteriolatic nephrosclerosis
447 other hypertensive disease without heart disease

ICD 8 Hypertensive disease B27 (401-405)

400 malignant hypertension
401 essential benign hypertension
402 hypertensive heart disease
403 hypertension with renal disease
405 secondary hypertension

ICD 9 Hypertensive disease AM27 (401-405)

401 essential hypertension
402 hypertensive heart disease
403 hypertensive renal disease
404 hypertensive heart and renal disease
405 secondary hypertension

Ischemic Heart Disease

ICD 7 Arteriosclerotic and degenerative heartdisease (420-422)

420 arteriosclerotic heart disease, incl. coronary disease
421 chronic endocarditis, not specified as rheumatic
422 other myocard degeneration

ICD 8 Ischemic heart disease B28 (410-414)

410 acute myocardial infarction
411 other acute and subacute forms of ischemic heart disease
412 chronic ischemic heart disease
413 angina pectoris
414 asymptomatic ischemic heart disease

ICD 9 Ischemic heart disease AM28+AM29 (410-414)

410 acute myocardial infarction
411 other acute and subacute forms of ischemic heart disease
412 old myocardial infarction
413 angina pectoris
414 other forms of chronic ischemic heart disease

Other forms of heart disease

ICD 7 Other diseases of the heart and diseases of the veins (430-434, 450-468, 782)

430 acute and subacute endocarditis
431 acute myocarditis and not-specified as rheumatic
432 acute pericarditis specified as not rheumatic
433 functional disease of the heart
434 other not specified diseases of the heart
450 general arteriosclerosis
451 aneurysm of the aorta, not syfilitic and aneur. diss.
452 other aneurysm, except from the heart and aorta
453 periferic vascular disease
454 arterial embolism and thrombosis
455 gangrene without specific cause
456 other diseases of the veins
782 symptoms of the cardiovascular and lymphatic system

ICD 8 Other forms of heart disease (420-429,440-458)

420 acute pericarditis, specified as nonrheumatic
421 acute and subacute endocarditis
422 acute and subacute myocarditis
423 chronic disease of pericardium, specified as nonrheumatic
424 chronic disease of endocardium (arterioscl.)(hypert.)
425 cardiomyopathy (myocardiopathy)
426 pulmonary heart disease
427 symptomatic heart dis. (cardiac arrest, block, fibrill)
428 other myocardial insufficiency
429 ill-defined heart disease
diseases of arteries, arterioles and capillaries (440-448)
440 arteriosclerosis
441 aortic aneurysm
442 other aneurysm
443 other peripheral vascular disease
444 arterial embolism and thrombosis
445 gangrene
446 polyarteritis nodosa and similar conditions
447 other disease of arteries and arterioles
448 disease of capillaries
diseases of veins and lymphatics, and other diseases of circulatory system (450-459)
450 pulmonary embolism and infarction
451 phlebitis and thrombophlebitis
452 portal vein thrombosis
453 other venous embolism and thrombosis
454 varicose veins of lower extremities
455 hemorrhoids
456 varicose veins of other sites
457 noninfective diseases of lymphatic channels
458 other diseases of circulatory

ICD 9 Other forms of heart disease

diseases of pulmonary circulation (415-417)
415 acute pulmonary heart disease
416 chronic pulmonary heart disease
417 other diseases of pulmonary circulation
other forms of heart disease (420-429)
420 acute pericarditis
421 acute and subacute endocarditis
422 acute myocarditis
423 other diseases of pericardium
424 other diseases of endocardium
425 cardiomyopathy
426 conduction disorders
427 cardiac dysrhythmias
428 heart failure
429 ill-defined descriptions and complications of heart dis.
diseases of arteries, arterioles and capillaries (440-448)
440 arteriosclerosis
441 aortic aneurysm
442 other aneurysm
443 other peripheral vascular disease
444 arterial embolism and thrombosis
446 polyarteritis nodosa and allied conditions

447 other disorders of arteries and arterioles
448 disease of capillaries
diseases of veins and lymphatics, and other diseases of circulatory system (451-459)
451 phlebitis and thrombophlebitis
452 portal vein thrombosis
453 other venous embolism and thrombosis
454 varicose veins of lower extremities
455 hemorrhoids
456 varicose veins of other sites
457 noninfectious disorders of lymphatic channels
458 hypotension
459 other disorders of circulatory system

Cerebrovascular disease

ICD 7 Cerebrovascular disease (B22)

330 subarachnoid hemorrhage
331 cerebral hemorrhage
332 cerebral embolism/occlusion
333 spasm of cerebral arteries
334 other and ill-defined cerebrovascular disease

ICD 8 Cerebrovascular Disease (B30)

430 subarachnoid hemorrhage
431 cerebral hemorrhage
432 occlusion of precerebral arteries
433 cerebral thrombosis
434 cerebral embolism
435 transient cerebral ischemia
436 acute, but ill-defined, cerebrovascular disease
437 generalized ischemic cerebrovascular disease
438 other and ill-defined cerebrovascular disease

ICD 9 Cerebrovascular Disease (AM30)

430 subarachnoid hemorrhage
431 intracerebral hemorrhage
432 other and unspecified intracranial hemorrhage
433 occlusion and stenosis of precerebral arteries
434 occlusion of cerebral arteries
435 transient cerebral ischemia
436 acute, but ill-defined, cerebrovascular disease
437 other and ill-defined cerebrovascular disease
438 late effects of cerebrovascular disease

Influenza

ICD 7 Influenza (480-483)

480 influenza with pneumonia
481 influenza with other not specified
482 influenza with disease of digestive system
483 influenza with disease of nervous system

ICD 8 Influenza (470)

470 influenza

ICD 9 Influenza (487)

487 influenza

Pneumonia

ICD 7 pneumonia (490-493)

490 lobular pneumonia
491 bronchopneumonia
492 primary unspecified pneumonia
493 other not specified pneumonia

ICD 8 Pneumonia (480-486)

480 viral pneumonia
481 pneumococcal pneumonia
482 other bacterial pneumonia
483 pneumonia due to other specified organism
484 acute interstitial pneumonia, organism not specified
485 bronchopneumonia, organism not specified
486 pneumonia, organism and type not specified

ICD 9 Pneumonia (480-486)

480 viral pneumonia
481 pneumococcal pneumonia
482 other bacterial pneumonia
483 pneumonia due to other specified organism
484 pneumonia in infectious disease classified elsewhere
485 bronchopneumonia, organism unspecified
486 pneumonia, organism unspecified

Bronchitis, emphysema, and asthma

ICD 7 Bronchitis (500-502)

500 acute bronchitis
501 not specified bronchitis
502 chronic bronchitis
783 symptoms due to respiratory organs

ICD 8 Bronchitis, emphysema, and asthma (489-493)

489 acute bronchitis and bronchiolitis
490 bronchitis, unqualified
491 chronic bronchitis
492 pulmonary emphysema
493 asthma

ICD 9 Chronic obstructive pulmonary disease and allied conditions (490-493)

490 bronchitis, not specified as acute or chronic
491 chronic bronchitis
492 emphysema
493 asthma

Statistics

Formula 1

During an observation period of I months i = 1,...,I the monthly observed number of deaths from a particular cause (influenza excluded) in a certain subpopulation of size N_i is assumed to be a Poisson distributed random variable with mean and variance equal to a parameter λ specified as

$$\lambda_i = N_i * \exp\left(\sum_{j=1}^{12} \alpha_j M_j + \sum_{k=2}^{K} \beta_k J_k + \gamma F_i \right)$$

i = 1,...,I (monthly figures)

N_i = size of the subpopulation considered in month i

M_j = 1 for calendar month j
= 0 elsewhere
j = 1,...,12 (January-December)

J_k = 1 for the k-th calendar year considered
= 0 elsewhere
(basis is first calendar year considered)
k = 2,...,K

F_i = influenza activity indicator in month i

The coefficients α_j , β_k and γ have to be estimated.

Formula 2

Special interest lies in the coefficient γ which represents the effects of the influenza activity in the total population on mortality from a certain cause other than influenza in a certain subpopulation.
The quantity $1-\exp(-\gamma F_i)$ represents the excess mortality in month i as proportion of λ_i.

As a first approach to measure influenza-activity, F_i is defined as the influenza-mortality rate per month during the period 1-1967 to 6-1989 in the total population.

The model as it stands above is only specified for one death cause category and one subpopulation considered. In order to indicate the various death cause categories and subpopulations (age groups) considered two more indices are necessary : d for death cause category (d = 1,...,D) and p for subpopulation (p = 1,...,P). In the model the coefficients α, β and γ as well as the expected number λ should get additional indices d and p:

$$\alpha_{jdp}\ ,\ \beta_{kpd}\ ,\gamma_{dp} \text{ and } \lambda_{idp}.$$

The size N of the subpopulation considered should only get an additional index p : N_{ip}.

Hence, the model becomes:

$$\lambda_{idp} = N_{ip} * \exp\left(\sum_{j=1}^{12} \alpha_{jdp} M_j + \sum_{k=2}^{K} \beta_{kdp} J_k + \gamma_{dp} F_i \right)$$

for the d-th death cause category (d=1,...,D) and the p-th subpopulation (p=1,...,P)

Formula 3

In the whole study (22.5 years) the number of registered influenza deaths in The Netherlands equals

$$\sum_{i=1}^{270} F_i = 9710$$

Formula 4

The estimated number of excess deaths over the whole study period associated with influenza activity can be obtained from the model as:

$$\sum_{i=1}^{270} \hat{\lambda}_i \{1 - \exp(-\hat{\gamma} F_i)\} = 25101$$

Formula 5

Using the regression model for subpopulations (age groups) p, it can be estimated which proportion of excess mortality can be attributed to a certain age group p. The denominator of this proportion is the number of 25101 as given above. The numerator is excess mortality in age group p and equals

$$\sum_{i=1}^{270} \hat{\lambda}_{ip} \{1 - \exp(-g\hat{\gamma}_p F_i)\}$$

where $\hat{\gamma}_p$ is the estimated effect of influenza F_i in age group p and $\hat{\lambda}_{ip}$ is the predicted total mortality (excl. influenza) in month i in age group p.

Formula 6

The part of total mortality per month that is associated with influenza is the predicted total influenza (related) mortality

$$F_i + \hat{\lambda}_i \{1 - \exp(-\hat{\gamma} F_i)\}$$

as proportion of predicted total mortality

formula 7

$$F_i + \hat{\lambda}_i$$

Formula 8

The percentage of excess (influenza related) mortality of total mortality (influenza excluded) in a season year can be calculated as:

$$100 \frac{\sum_{i=7}^{18} \hat{\lambda}_{ip} \{1 - \exp(-\hat{\gamma}_p F_i)\}}{\sum_{i=7}^{18} \hat{\lambda}_{ip}}$$

where p denotes age group and months 7 to 18 constitute the season year 1967/68.

Formula 9

The average percentage over all 22 season years in the total population is

$$\frac{100 \sum_{i=7}^{270} \hat{\lambda}_{ip} \{1 - \exp(-\gamma_p F_i)\}}{\sum_{i=7}^{270} \hat{\lambda}_{ip}}$$

Formula 10

The excess (influenza related deaths) mortality per million inhabitants per age-group per season-year is calculated as:

$$\frac{10^6 \sum_{i=7}^{18} \hat{\lambda}_{ip} \{1 - \exp(-\gamma_p F_i)\}}{\sum_{i=7}^{18} N_{ip}/12}$$

where p denotes age group 60-69 and the denominator is the mean population size aged 60-69 in the season-year 1967/68.

Formula 11

In order to indicate the various diagnostic categories and subpopulations (age groups) considered two indices are necessary : n for diagnostic category (n = 1,...,N) and p for subpopulation (p = 1,...,P). In the model the coefficients α, β and γ as well as the expected number λ should get indices d and p:

$$\alpha_{jnp}\ ,\ \beta_{knp}\ ,\ \gamma_{np} \text{ and } \lambda_{inp}.$$

The size N of the subpopulation considered get an additional index p : N_{ip}.
Hence, the model becomes:

$$\lambda_{inp} = N_{ip} * \exp\left(\sum_{j=1}^{12} \alpha_{jnp} M_j + \sum_{k=2}^{K} \beta_{knp} J_k + \gamma_{np} F_i \right)$$

for the n-th diagnostic category (n=1,...,N) and the p-th subpopulation (p=1,...,P).

The estimated γ coefficients of four age groups and eight death causes (including all causes).

	scaled deviance (x^2 235 df)	p	estimated coefficient γ	SE	correction factor for SE*	Z= coeff/ corr.SE
total	2070.7	p<0.01	0.0002637	7.522e-06	2,97	11,81
tot6	403.38	p<0.01	0.0002513	0.00001750	1,31	10,96
tot7	807.44	p<0.01	0.0003037	0.00001366	1,85	12,02
tot8	1651.1	p<0.01	0.0003462	0.00001302	2,65	10,03
crhtot	314.86	p<0.01	0.0002326	0.00009133	1,16	2,20
crh6	255.05	p=0.18	0.0004828	0.0001728	1,04	2,69
crh7	288.76	p<0.01	0.0003885	0.0001663	1,11	2,10
crh8	261.43	p=0.11	0.00002963	0.0002398	1,05	0,12
hyptot	275.47	p<0.05	0.0004036	0.00007464	1,08	5,01
hyp6	238.18	p=0.43	0.0002380	0.0001842	1,01	1,29
hyp7	253.76	p=0.19	0.0003835	0.0001265	1,04	2,92
hyp8	225.24	p=0.66	0.0004605	0.0001202	0,98	3,83
ihztot	722.45	p<0.01	0.0002465	0.00001593	1,75	8,84
ihz6	403.47	p<0.01	0.0002647	0.00003343	1,31	6,04
ihz7	435.64	p<0.01	0.0002778	0.00002703	1,36	7,56
ihz8	472.81	p<0.01	0.0002991	0.00002945	1,42	7,15
ohztot	927.78	p<0.01	0.0004747	0.00002644	1,99	10,18
ohz6	362.05	p<0.01	0.0004374	0.00008544	1,24	4,13
ohz7	391.76	p<0.01	0.0005429	0.00004848	1,29	8,68
ohz8	766.98	p<0.01	0.0004500	0.00003534	1,81	7,04
cvatot	602.23	p<0.01	0.0002324	0.00002247	1,60	6,46
cva6	236.96	p=0.45	0.0002374	0.00006160	1,00	3,85
cva7	404.64	p<0.01	0.0001976	0.00003801	1,31	3,97
cva8	488.55	p<0.01	0.0003083	0.00003342	1,44	6,41
pnetot	1597.7	p<0.01	0.001147	0.00004023	2,61	10,92
pne6	334.71	p<0.01	0.001325	0.0001543	1,19	7,22
pne7	592.17	p<0.01	0.001372	0.00007844	1,59	11,00
pne8	1311.1	p<0.01	0.001005	0.00005190	2,36	8,21
beatot	625.79	p<0.01	0.0008831	0.00003895	1,63	13,91
bea6	300.18	p<0.01	0.001011	0.00008060	1,13	11,10
bea7	438.62	p<0.01	0.0009412	0.00006422	1,37	10,70
bea8	426.43	p<0.01	0.0007805	0.00007085	1,35	8,16

*) correction factor = square root (scaled deviance/df)

GLIM 3.77 update 0 (copyright)1985 Royal Statistical Society, London

Independent variables:

influenza	number of influenza death cases registered by C.B.S. in total population per month
month	first month 1, last 12
year	first is 1967=1, last 1989=23
population	total Dutch population in millions

Dependent variable:

total number of death cases per month given by the C.B.S. without influenza death cases.

```
i ? $units 270$
i ? $data jr md inftot tot poptot$
i ? $dinput 5 80$
i      1.00     1.00    30.00   8814.00    12.54
i      1.00     2.00    26.00   7769.00    12.54
i      1.00     3.00    23.00   8139.00    12.54
i      1.00     4.00    15.00   8122.00    12.54
i      1.00     5.00     7.00   8344.00    12.54
i      1.00     6.00     6.00   7992.00    12.54
i      1.00     7.00    12.00   8256.00    12.54
i      1.00     8.00    10.00   7843.00    12.54
i      1.00     9.00    11.00   8114.00    12.54
i      1.00    10.00     6.00   8327.00    12.54
i      1.00    11.00    11.00   8495.00    12.54
i      1.00    12.00    53.00   9343.00    12.54
i      2.00     1.00   413.00  10492.00    12.66
etc

i ? $factor md 12 jr 23$
i ? $cal logpopt=%log(poptot)$
i ? $offset logpopt$
i ? $yvar tot$
i ? $error p$
i ? $link l$
i ? $fit md+jr+inftot-1$

o scaled deviance = 2070.7 at cycle  3
o         d.f. =  235
o
```

```
i ? $dis ler$
o Linear predictor:
o
o  terms =  MD + JR + INFT
o
o          estimate       s.e.    parameter
o    1        6.562   0.003853      MD(1)
o    2        6.464   0.003821      MD(2)
o    3        6.540   0.003767      MD(3)
o    4        6.471   0.003789      MD(4)
o    5        6.487   0.003782      MD(5)
o    6        6.452   0.003805      MD(6)
o    7        6.466   0.003823      MD(7)
o    8        6.441   0.003840      MD(8)
o    9        6.422   0.003852      MD(9)
o   10        6.492   0.003805     MD(10)
o   11        6.495   0.003803     MD(11)
o   12        6.572   0.003752     MD(12)
o   13      0.01985   0.004455      JR(2)
o   14      0.02873   0.004442      JR(3)
o   15      0.03076   0.004441      JR(4)
o   16      0.05111   0.004376      JR(5)
o   17      0.05823   0.004358      JR(6)
o   18      0.01613   0.004404      JR(7)
o   19     0.005376   0.004394      JR(8)
o   20      0.02750   0.004366      JR(9)
o   21      0.01303   0.004400     JR(10)
o   22    -0.002747   0.004380     JR(11)
o   23      0.01912   0.004349     JR(12)
o   24      0.01148   0.004356     JR(13)
o   25      0.02394   0.004337     JR(14)
o   26      0.02603   0.004326     JR(15)
o   27      0.03355   0.004312     JR(16)
o   28      0.03248   0.004307     JR(17)
o   29      0.04568   0.004290     JR(18)
o   30      0.06602   0.004267     JR(19)
o   31      0.07287   0.004253     JR(20)
o   32      0.05284   0.004271     JR(21)
o   33      0.06323   0.004256     JR(22)
o   34      0.07583   0.005111     JR(23)
o   35    0.0002637  7.522e-06       INFT
o    scale parameter taken as  1.000
o
o  unit  observed     fitted   residual
o     1      8814      8947.     -1.409
o     2      7769      8104.     -3.721
o     3      8139      8738.     -6.412
o     4      8122      8137.     -0.171
o     5      8344      8247.      1.066
o     6      7992      7962.      0.337
o     7      8256      8091.      1.836
o     8      7843      7883.     -0.455
etc
```

Influenza: Prediction of mortality by morbidity parameters, in The Netherlands in the period 1970-1989

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This chapter has been submitted

Introduction

The general practitioner has a key role in providing information about infection patterns[1]. This information can be used for resource allocation in public health planning and to evaluate control and prevention measures[2345]. This is especially true for influenza, caused by influenza A or B viruses and occurring as local or widespread epidemics, occasionally as pandemics. The impact of influenza on the overall mortality (specially among the elderly and chronically ill persons), and on the morbidity of a population (occupancy of health institutions, disruptive effects on schools and industry, etc.) has been extensively described[6]. Recently, it has become evident that influenza may cause substantial "excess mortality" beside the "regular mortality"[1789]. Although influenza is almost impossible to control, it is important to monitor the progress and impact of the disease in order to provide an early warning to the national and international community and to allow time for appropriate vaccines to be manufactured and distributed or other prophylactic measures to be taken.

In The Netherlands, a country of 14.9 million inhabitants, a network of so-called "sentinel stations" or "spotters" has been working since 1970. About fifty practitioners have been asked to keep a weekly account of the number of patients presenting themselves with certain diseases, among others influenza-like illness (ILI).
The purpose of this study is to investigate what kind of relationship can be established between the weekly influenza-like illness registered by the general practitioners and the monthly influenza-mortality, and to predict the influenza-mortality.

Materials and Methods

Influenza mortality
The measure of influenza-mortality is the overall influenza- mortality (International Classification of Diseases (ICD) 9th revision: AM 34) (primary cause of death) per month given by the Dutch Central Bureau of Statistics during the period 7-1970 to 6-1989, expressed per million population size.

Influenza morbidity
In the Netherlands a network of sentinel stations was instituted in 1970 by The Netherlands Institute for General Practice, The Ministry of Social Affairs and Public Health, The Chief Medical Office of Health and the Prevention Fund. Influenza-like illness (ILI) is registered by 50 general practitioners throughout the country every week from Monday to Friday. ILI must satisfy the following criteria:

a. An acute beginning, i.e. at most a prodromal stage of three to four days.
b. The infections must be accompanied by a rise in rectal temperature to at least 38°C.
c. At least one of the following symptoms must be present: cough, coryza, sore throat, frontal headache, retrosternal pain and myalgia.

The data are provided in rates per 10,000 of the practice population per week, during the period 1970 to 1989.

Time interval

Since mortality is expressed in monthly figures, and morbidity in weekly figures, and since it is difficult to combine calendar weeks into calendar months, we choose a whole year as common time interval for further calculations. According to the epidemiology of influenza in the Netherlands (occurrence virtually always in the winter), a season-year is used, starting in July of one year and ending in June of the following year.

Parameters

Mortality is expressed by the sum of the 12 monthly mortality figures in each season-year.

Morbidity is expressed by three summary parameters , deduced from the 52 (or 53) weekly ILI-figures, (i.) their sum (i.e. global extent of an epidemic), (ii.) their standard deviation, and (iii.) their maximum (i.e. peak number of ILI during an epidemic). These three parameters are mutually compared with respect to their predictability for total mortality in the 19 season-years available.

Regression analysis

Regression analysis was performed using the SPSS/PC+ package. The assumption is that there is a log-linear relationship between y, the "dependent" variable and an "independent" variable X.
The model used was:

$$\ln Y = A + BX + e$$

where ln Y is the natural logarithm of influenza mortality, A is a constant, B the regression coefficient of X on ln Y and X one of three alternative summary parameters for influenza morbidity.
In addition, there is assumed to be a random component in the fluctuation of ln Y given by the normally distributed error term e. The constant A and regression coefficient B are estimated by the method of least squares.
From a residual analysis it appeared that the natural logarithm of mortality was preferable as the variable to be explained, instead of mortality itself.

The mortality/illness peak level-ratio will be calculated as the expected influenza mortality in a season year divided by the peak level X of ILI in that particular season year. In formula:

$$E(Y)/X = \exp(A + BX + s^2/2) / X \quad (s=\text{sigma})$$

E = expected
where s^2 is the variance of the error term e

Results

In Figure 1 the number of influenza-like illness per week and the influenza-mortality per month are presented for the entire period 1970-1989. The mortality peaks occur simultaneously with the illness peaks. With the aid of a regression analysis we tried to explain the relationship between mortality and morbidity per season-year. Table 1 presents the three summary parameters (sum of ILI per 10,000 over the season-year, standard deviation and maximum), the observed influenza mortality per million per year, predicted mortality using the three summary parameters. Table 2 shows the result of three regression analyses each using one of the summary parameters. Surprisingly, the extent of the epidemic (sum of ILI-figures) is not powerful to predict mortality (R^2 = 0.52, only). When using the peak number of ILI, the R^2 increases to 0.71. The standard deviation, however, is the best parameter to explain the relationship with mortality (R^2 =0.78). Some other secondary parameters, such as the skewness and the range, combinations of parameters or second order terms did not significantly improve the results (not shown).

Table 1 Observed influenza morbidity (ILI per 10.000 per season-year) with the three summary parameters (sum, standard deviance and maximum), observed influenza mortality per million per year and predicted mortality using the three summary parameters.

season	observed morbid.			obs	predicted mortality		
	sum	st.dev.	max.	mort	sum	st.dev.	max.
70-71	776	8.22	47	16	48	12	4
71-72	863	17.34	64	46	65	45	5
72-73	758	20.72	115	74	45	74	117
73-74	816	16.51	78	26	55	40	41
74-75	847	19.22	90	53	61	59	57
75-76	687	16.96	68	86	35	42	30
76-77	554	10.15	44	18	22	16	15
77-78	721	22.67	107	38	39	99	93
78-79	502	7.58	42	8	18	11	14
79-80	451	3.73	15	5	15	6	7
80-81	486	8.47	36	6	17	12	12
81-82	390	4.25	20	5	12	6	8
82-83	508	9.76	42	15	19	15	14
83-84	501	11.55	53	15	18	19	20
84-85	465	11.07	54	13	16	18	20
85-86	601	16.00	71	34	26	37	33
86-87	275	5.86	26	6	8	8	9
87-88	154	3.48	9	3	5	6	6
88-89	312	9.88	45	42	9	15	16

Fig. 1 Influenza mortality per month per million population and influenza-like illness per week per 10.000 population with the epidemic influenza-strain. ..... mortality (left scale) _____ illness (right scale)

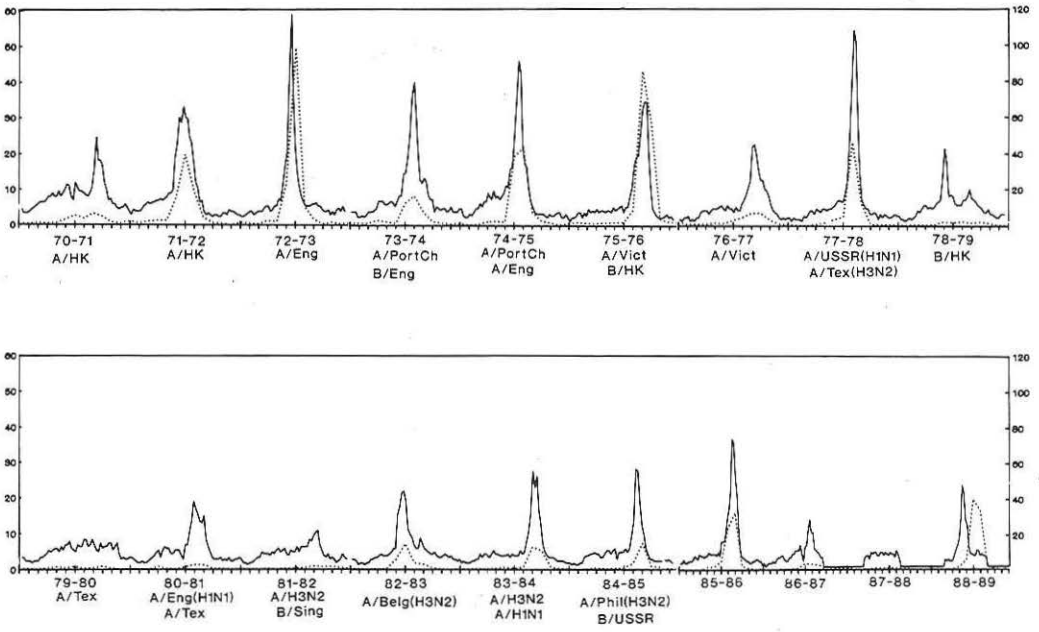


Table 2 Results of three regression analyses, to explain the logarithm of total influenza mortality, each using one of the following three summary parameters of the 52 (or 53) weekly influenza figures as explanatory variables, viz., the sum of illness, standard deviation and maximum.

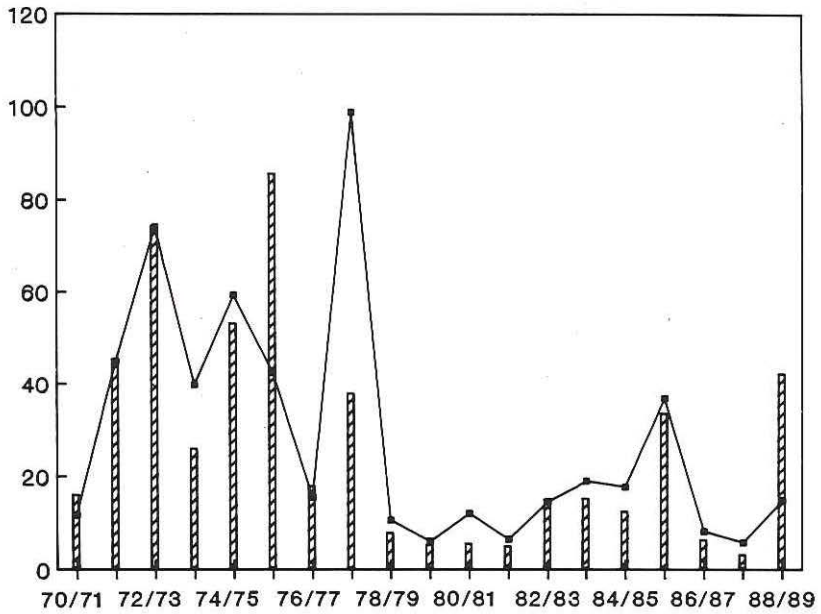
Explanatory variable	R^2	Constant (interc.	Beta (slope)	S.E. of beta
maximum	0.71	1.31	0.029	0.0044
standard deviation	0.78	1.12	0.148	0.0191
sum of illness	0.52	0.89	3.52E-3	0.0082

R^2 is the proportion of variance of influenza mortality that is explained by a log linear relationship with one of the summary parameters.

S.E. measure of scatter about the regression line

In first instance we examine the relation between influenza mortality and influenza-like illness as expressed by the standard deviation of the weekly ILI-numbers, as the strongest predictor of mortality (see Figure 2).

Fig. 2 Observed influenza-mortality per season-year per million population and predicted mortality using the standard deviation.
bar: observed mortality ____ predicted mortality



The mortality in the seasons 1970-71, 1971-72 and 1972-73 is correctly predicted. In the season 1972-73 the mortality is high. The reason for this could be the new strain A/England(H3N2) which appeared after the 4 year A/Hong Kong period[10].

In 1973-74 mortality is less than predicted. In the U.K. the A/England strain was replaced by A/Port Chalmers. The pattern of influenza infection was rather unusual in this epidemic. Both influenza A and B were circulating and the influenza A epidemic had a very prolonged course[11]. In The Netherlands the strain isolated at most was B/England and caused less mortality than predicted[12]. An explanation could be that the influenza B causes a lot of mild influenza-illness but relatively less mortality in this season.

It is striking that the wave of A/Port Chalmers causes a lot of mortality in 1974-75 but was predicted by the model.

In 1975-76 the A/Victoria arrives and causes high mortality, much higher than predicted by the model. The A/Victoria showed considerable drift from the A/Port Chalmers. The effect was that the virus could spread throughout the country.

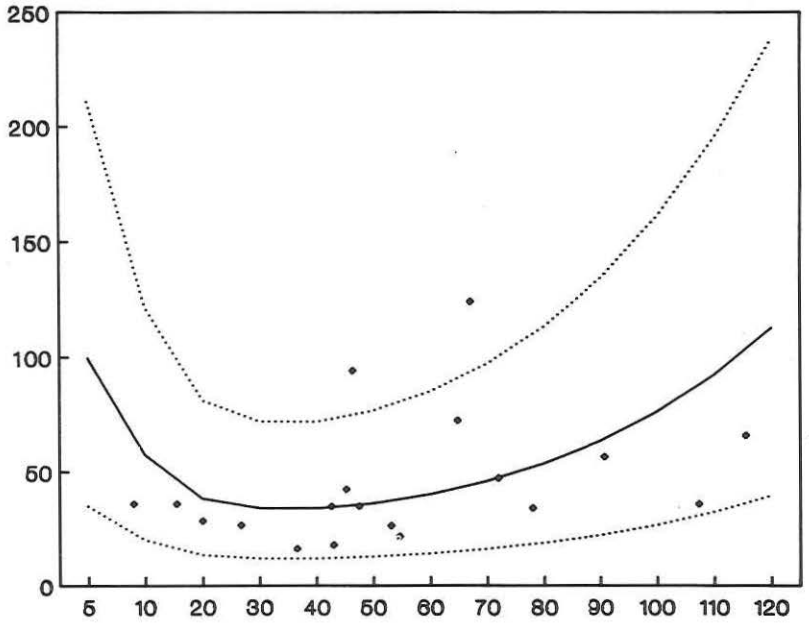
The next year (1976-77) the same virus circulated but caused less mortality due to the immune status from the year before. In 1977-78 the A H1N1 reappeared, and circulated in the world for 10 years between 1947 and 1957[13]. Figure 2 shows that this virus generated much morbidity, but less mortality. In general, the usual (excess) mortality mostly occurs in the elderly[8]. Older people (>30 years old) had already antibodies to this strain[14]. The virus was isolated particularly in young people, so this could be the reason that this strain caused less mortality than predicted[15] [16].

In the next years the influenza epidemics are less striking except the last epidemic 1988-89. This epidemic caused in The Netherlands more mortality than predicted. The reason could be that two A strains (H1N1 and H3N2) and the B virus were epidemic[17].

A drawback of the standard deviation of the weekly ILI-figures is that this parameter can only be obtained after the end of the season-year, i.e. a long time after the winter epidemic. More attractive is the peak number of ILI, since this parameter is already available during an ongoing epidemic. The proportionality relationship between mortality and the illness peak level can be expressed by a ratio defined as the number of mortality cases in a year per illness case when illness takes its peak in that year. This ratio is dependent on the size of the peak as follows from the specified loglinear relationship between mortality and the peak level.

Figure 3 shows this predicted mortality/illness ratio with the 5th and 95th percentile lines obtained from the estimated residuals.
The observed mortality/illness ratios are also presented as 19 scatter points. Two mortality/illness ratios exceed the 95th percentile, i.e. A/Victoria in 1975-76 and in 1988-89 three epidemic strains. These two epidemics caused proportionally high mortality. It is seen that, if the peak reaches a level of 35 cases influenza-like illness per 10.000 per week, the (predicted) ratio is at its lowest level. The threshold of 35 equals by definition the reciprocal of the estimated beta-coefficient (slope of the regression line) of 0.029 in table 1. Therefore the "impact" of influenza at an illness peak-level of 35 is relatively low. Exceeding this threshold-level, the impact of influenza increases more than proportionally.

Fig. 3 Influenza Mortality/Illness ratio by different levels of the maximum with 5th and 95th percentile lines
____ predicted mortality/illness ratio .... percentile lines
+ observed ratios (19 seasons)



Discussion

In this study, a model constructed to define the relationship between morbidity and mortality of influenza in a defined place and time period, is presented.

It is shown that the maximum number of influenza-like illness in a week is a better prognostic parameter to estimate the impact of influenza on the number of deaths (after logarithmic transformation), than the global extent of the epidemic (total number of influenza-like illness during the 52 or 53 weeks of the epidemic-year). The standard deviation of the number of influenza-like illness over the 52 or 53 weeks is the best parameter to explain the relationship between morbidity and mortality, but not a very practical one.

An implication from the loglinear relationship of mortality with the illness peak is that the mortality/illness ratio varies with the size of the peak over the season years. It is possible to calculate a threshold beyond which (from both directions) the mortality increases more than proportionally to the peak-level of illness. There are at least two interpretations for this mathematical phenomenon. First, high peaks of influenza morbidity cause relatively high mortality because the virus is not only spreading very quickly, but is also more virulent (i.e. lethal). Second, more probably, if the influenza-activity (i.e. peak-level) is high, the total number of influenza-like illness is underreported. It is very plausible that if one member of a family has influenza and visits the general practitioner, the next members of that family will not visit him, leading to underreport ILI. Morbidity is underreported if it exceeds a threshold (in this study about 35 cases per 10.000 per week) or the associated- mortality of the epidemic indeed increases more than proportionally after reaching the threshold.
So far, we only discussed the plausibility of a postulated model, particularly its mathematical implications. Empirical evidence supporting those implications is still very limited as appears from inspection of the 19 observations scattered in Figure 3.

Tillett and Spencer[18] used the "cusum" technique to conclude that the general practitioners indices were helpful to describe both size and timing of the epidemics. The conclusions are in accordance with ours but they did not use "summary parameters" which reflect characteristics of the epidemic.

It is clear that no system of data collection can be perfect[19]. One reason lies in the biological nature of the influenza viruses with their constantly changing membrane proteins (antigenic drift) and the occasional occurrence of new subtypes or types (antigenic shift). It is well known that each subtype of influenza can have its own pattern of morbidity and mortality[15]. Probably the model could improve its reliability by addressing the type/subtype of the circulating influenza viruses. In this study it was not possible because there are no reliable data on the distribution of the number of influenza A (and subtypes H1/H3) and influenza B.

Another reason concern the behavior of the population. Not all patients seek advice, especially within one family, resulting in marked underreporting. This drawback is compensated to some extent by the fact that the interpretation of data is commonly based on the incidence in one period as compared to another[20].

To what extent do the ILI-numbers as reported by the general practitioners, reflect the real extent of influenza morbidity? Flemming and Ayres[21] conclude that in general practice the distinction between influenza and influenza-like illness is reliable. At this point more research has to be done also for the Dutch situation. The Weekly Returns Service of the Royal College of General Practitioners in the U.K. distinguishes between "Influenza" and "Influenza like illness". The choice between these diagnoses is made by discrimination[22]. In our method no distinction is made between these diagnoses. Without any laboratory confirmation it is hard to do this.

A disadvantage of a surveillance system based upon sentinel stations, despite the efforts made by the general practitioners, is the inertness. The ILI-figures are at the earliest available one and a half week after the collection. So the system can improve its effectiveness by computerizing. In France such an electronic system was set up in 1984[23]. Each general practitioner electronically transfers data to the coordinating centre using the ordinary telephone network and terminals supplied by the Direction Generale des telecommunications. Any general practitioner in the network can receive at any time weekly surveillance bulletins that are displayed. Besides epidemiological news, the network includes also information about immunization schedules.

Hannoun et al[24]. introduced also other parameters in the surveillance system (drug prescription, absence from work etc) which improve the sensitivity of the surveillance system.

We believe that a good "direct" surveillance system based upon direct communication between general practitioners and the National Influenza Centre is an important tool in the prevention of the influenza related morbidity and mortality. This study indicates that the weekly number of influenza-like illness is a good prognostic parameter for the real impact of influenza. An electronic surveillance system could detect immediately the threshold after which the influenza mortality increases more than proportionally, at least if our model is valid. Reaching this level, electronic bulletins can stress the importance for prophylactic measures or, especially for the high-risk patient[25], the combination with amantadine or rimantadine to prevent excess mortality.
The benefits of such an electronic surveillance system are not restricted to the epidemic. We believe that such a system can improve the involvement of general practitioners in the surveillance of influenza and by this way improve the awareness of the consequences of influenza, possibly resulting in a higher degree of vaccination.

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Unexpected High Influenza Related Excess Mortality in The Netherlands (1989-1990)

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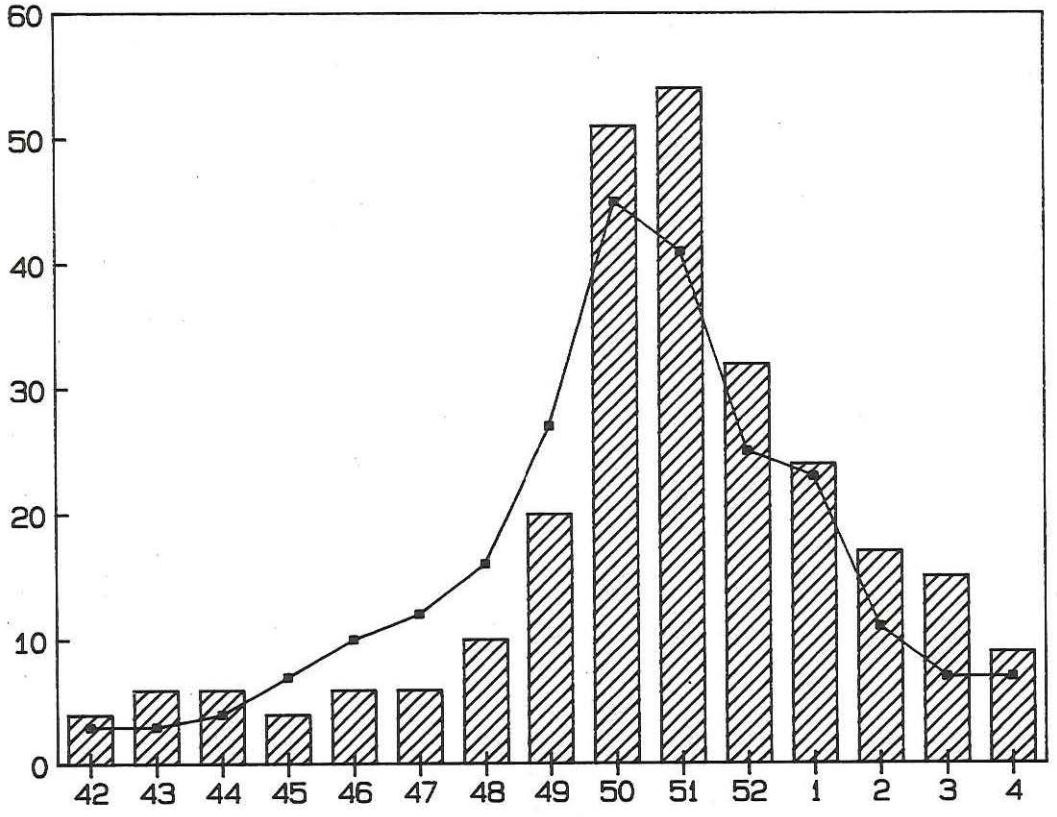
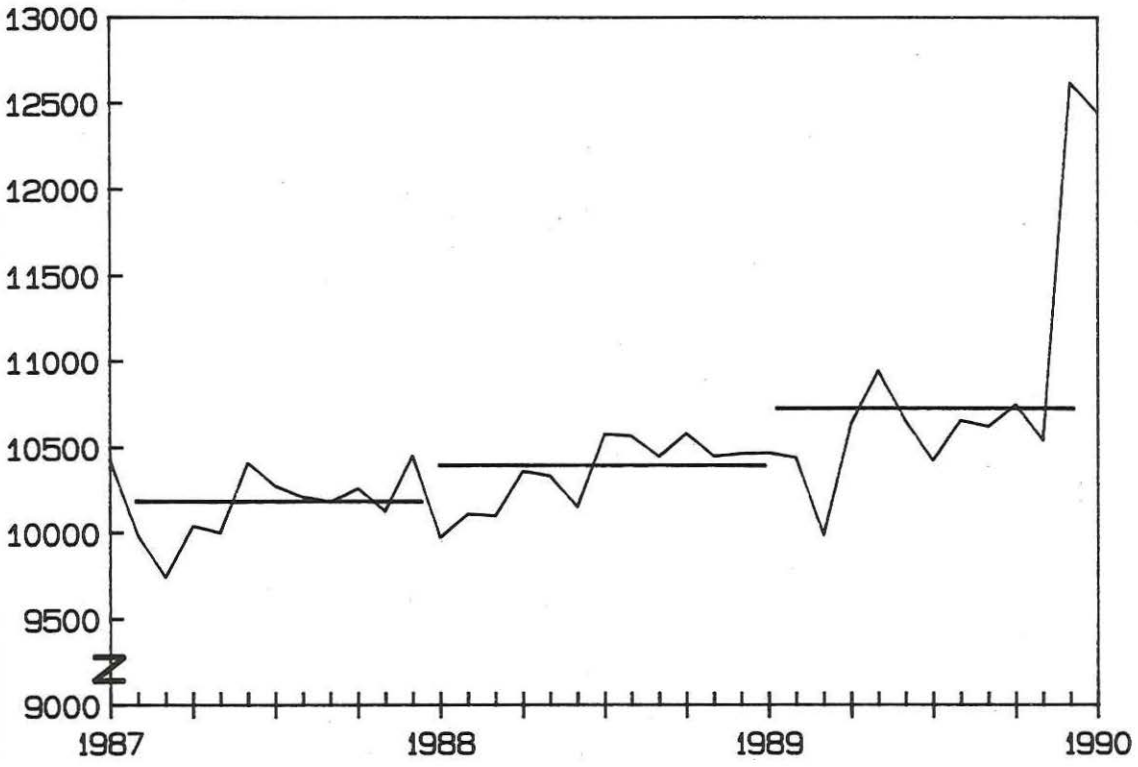
The number of weekly influenza-like illnesses (ILI), as reported by general practitioners, randomly distributed over The Netherlands, started to increase at the beginning of December 1989 and reached a peak of 54 per 10 000 inhabitants around Christmas. This pattern resembles that experienced in 1988/89 and in earlier epidemics (see Fig. 1)

Fig. 1 Influenza-like illness per 10 000 inhabitants per week in The Netherlands. Line: season 1988-1989, bar: 1989-1990.
Horizontal axis shows winter week numbers 42 to 4.
X-ax: weeknumbers (source: GHI-NIVEL)



Unexpectedly the Netherlands Central Bureau of Statistics recorded a considerable increase in total mortality in December, 1989, and January 1990[1]. The daily number of deaths rose from the expected mean of 370 (in the total population) to over 400 during the influenza period and reached 500 in the second week of January (see Fig 2).

Fig. 2 Deaths per month, seasonally adjusted, in The Netherlands.
horizontal lines: annual average (source: CBS)



Mortality in these 2 months rose 18%, the increase being most pronounced in people over 80 years old (26%). The excess deaths totalled 4100 (0.3 per 1000 population). In the winters 1988-1989 and 1987-1988 no excess mortality was registered.

An unexpected excess mortality of 0.5 per 1000 has also been reported in the UK[2] where it was associated with influenza.

The predominant influenza strain throughout the 1989/90 epidemic was A/Shanghai/11/87(H3N2)-like. Haemagglutinin[3] and neuraminidase antigenic make-ups demonstrate that this strain is almost identical to the vaccine-strain[4] and the epidemic strain of 1988-1989.

Sera of 100 inhabitants, selected at random, collected before the epidemic of 1988-1989 and another 100 found before the epidemic of 1989-1990 were tested simultaneously against vaccine strain A/Shanghai/11/87(H3N2 and against two strains isolated during the two epidemics in The Netherlands. Protection was more prevalent before the latest epidemic than it was before the epidemic of 1988/89.

Table 1: per cent of 200 human pre-epidemic sera with protective antibodies (titre >100[5]) against the vaccine strain, the Dutch epidemic strains of 1988-1989 and 1989-1990

	A/Shanghai/ 11/87(H3N2)	A/Ned/ 501/88	A/Ned/ 620/89
human sera 1988	3 %	11 %	8 %
human sera 1989	10 %	25 %	20 %

Thus, in 1989-90 moderate influenza rates were attended by unusually high mortality, an observation that cannot be explained by a major antigenic drift, or by lack of antibody.
We suggest a change in biological activity as the cause[6].

We thank C.J.M. Prins, Dutch Central Bureau of Statistics, for his advice, and G.L. van der Water for technical assistance.

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General Conclusions

For many diseases mortality is an essential measure of incidence in epidemiologic studies. Its long-term trends form the basis for vital statistics. This is also valid for influenza research. In 1848 Farr described this in vivid detail for the epidemics in London in 1847. He introduced the concept of excess mortality, defining it as the number of deaths over and above the expected number for the particular season in which and place where the epidemic occurred.

In chapter 1 and 2 it was tried to assess the underreported effects of the epidemics of influenza on mortality in elderly people.

Although there is no definite proof of a causal relationship between influenza and excess mortality, it is clear from the estimates and figures that there is a strong association between influenza mortality and influenza related mortality.

In this study the excess mortality due to influenza has been estimated using a regression model based on four parameters: influenza-activity, month, year and population. The influenza-activity parameter which gave the best fit of the model is the influenza-mortality per month in the total population. No clear time-lag effect has been found which is taken as an indication that the major effect of influenza-activity on mortality for other causes does occur in the same month.

Our overall analysis indicated that one registered influenza death case is related with an overall 2.6 other death cases. This influenza related mortality occurs for 50% in the age group 60 - 79 and for the age group over 80 years 45% and only 5% in the age group under 60.

Almost half of the influenza related mortality is estimated to occur in the diagnostic group of heart diseases, about 25% in the group of lung diseases and about 30% in the remaining group of other mortality (not further defined).
In each diagnostic category (heart, lung and other) the age distribution is about the same with about 95% of the death cases in age group over 60 year.

Concerning the influenza related mortality in heart diseases the largest proportion occurs in the subgroup ischemic heart disease (44%), next, other heart diseases (30%) and third, cerebrovascular diseases (21%) whereas hypertensive heart disease and chronic rheumatic heart disease rank fourth (3%) and fifth (1%).

The proportion of influenza related mortality within subgroups by death cause is substantially the same. So the influenza related mortality is not associated with one particular heart disease.

In the diagnostic category of lung diseases the distribution of influenza related mortality in the subgroups by death cause, pneumonia and bronchitis/emphysema/asthma are fifty-fifty, when all ages are considered together. Within the two death cause subgroups the percentage influenza related mortality is the same in the various age groups.

During severe epidemics the proportion of influenza related mortality did reach a maximum level of 25%. This means a quarter of total mortality in all ages, in that particular month is related to influenza.

In the studied period (22.5 years) the average yearly direct mortality and related mortality for influenza turned out to be more than 2000 in people over 60 years in The Netherlands.

The idea that cold weather has an adverse effect upon people, sick or well, is easily appreciated. In this study no particular "weather factor" has been taken into account. Although this factor is partly incorporated into the month-correction factor.

In winter some viruses may become more active; for instance rhinovirus, coronavirus and parainfluenza virus. These viruses are supposed to usually cause a common cold (except parainfluenza 3) and are rarely a cause of severe illness. RS-virus and Mycoplasma pneumoniae can especially be important in children and elderly people. However, these agents cause an epidemic every winter so this phenomenon was included in our model by the month correction factor.

It is often suggested that influenza-related deaths are associated with patients who would have died from an underlying illness within a short period. From this study and many other studies it is clear that no complementary decline of mortality within a short period is recognized.
Tillet et al. examined the possibility that in winter influenza deaths could be followed by a deficit of summer deaths but they could not find a correlation, nor could demonstrate that high excess deaths in one winter tended to be followed by a deficit in the next winter. These observations suggest that excess deaths attributable to influenza do not in general shorten lives by a few months only.

Influenza has a larger impact on mortality than what is diagnosed under the death cause "influenza". The fact that these deaths have been coded as heart, lung or other mortality may have resulted partially from the incomplete information supplied by physicians completing death certificates. It may also result from the fact that the rules for classifying deaths under the International Classification of Diseases, Adapted (ICDA) usually give precedence to the underlying condition even when pneumonia is listed as the immediate cause.

For some death causes high values of the scaled deviance, i.e. in the upper 5% tail of its chi-square distribution are found. This warrants the conclusion that the model does not fit well enough. There is overdispersion (or extra-Poisson variation) in the data, probably due to unobserved heterogeneity caused by (unknown or unobserved) explanatory variables not incorporated into the model. Since the scaled deviance is proportional to the underlying monthly number of mortality cases and the population sizes, scaled deviance scores can become extremely high if there are model violations in a situation with very large numbers of observations per design point, as is the case here in some analyses.
However, the parameter estimates are still valid, since the standard errors of the estimated parameters are corrected in case of overdispersion.
From the residual analyses it is clear that no systemic error can be recogni. The residuals are distributed at random.

In this study no difference is made for the influenza-strain. There are no quantitative observation available. Clifford had some information about the antigenic drift although it gave little additional information.

Some studies were done to investigate the hypothesis that a virus could cause heart disease and even heart mortality. No clear evidence has been published so far about a direct relation between influenza and heart-disease. With regard to this aspect two observations in this study are important.
First, influenza related mortality only occurs, if it occurs at all, during the strict epidemic period. In all studies reviewed above, a virological agent was tried to find without particular reference to the influenza season.
Second, no death cause of the heart diseases is particular related to influenza. This observation suggests that there is no clear biological mechanism resulting in a specific biological defect, and therefore causing a specific death cause. But according to the, earlier mentioned, poor validity of registration of death cause in general, the same is likely to occur for the specific death cause of heart disease.
If there is indeed a relationship between influenza and heart-diseases, i.e. influenza causes heart deaths, the question is how this can be explained.

More research has to be done during an influenza epidemic to find the influenza virus or only a fragment of the RNA. Using new methods of molecular biology it could be possible to detect influenza virus out of the tractus respiratorius or other tissue.

It is likely that this analysis provided a conservative estimate of the potential full impact of influenza epidemics, because an appreciable proportion of the elderly and other high-risk persons received yearly influenza vaccine or at least prior to each of the epidemics included in the study. It is reasonable, therefore, to assume that thereby some excess deaths were in fact prevented.

In chapter 3 a model is tried to construct, to define the relationship between morbidity and mortality of influenza in a defined place and time period.

It is shown that the maximum number of influenza-like illness (ILI) in a week is a better prognostic parameter, to estimate the impact of influenza on the number of deaths, than the global extent of the epidemic (total number of influenza-like illness during the 52 or 53 weeks of the epidemic-year). The standard deviation of the number of influenza-like illness over the 52 or 53 weeks is the best parameter to explain the relationship between morbidity and mortality, but not a very practical one.

An implication from the loglinear relationship of mortality with the illness peak is that the mortality/illness ratio varies with the size of the peak over the season years. It is possible to calculate a threshold beyond which (from both directions) the mortality increases more than proportionally to the peak-level of illness. There are at least two interpretations for this mathematical phenomenon. First, high peaks of influenza morbidity cause relatively high mortality because the virus is not only spreading very quickly, but is also more virulent (i.e. lethal). Second, more probably, if the influenza-activity (i.e. peak-level) is high, the total number of influenza-like illness is underreported. It is very plausible that if one member of a family has influenza and visits the general practitioner, the next members of that family will not visit him, leading to underreport ILI. Morbidity is underreported if it exceeds a threshold (in this study about 35 cases per 10.000 per week) or the associated- mortality of the epidemic indeed increases more than proportionally after reaching the threshold.

It is clear that no system of data collection can be perfect. One reason lies in the biological nature of the influenza viruses with their constantly changing membrane proteins (antigenic drift) and the occasional occurrence of new subtypes or types (antigenic shift). It is well known that each subtype of influenza can have its own pattern of morbidity and mortality. Probably the model could improve its reliability by addressing the type/subtype of the circulating influenza viruses. In this study this was not possible because there are no reliable data on the distribution of the number of influenza A (and subtypes H1/H3) and influenza B.

Another reason concerns the behavior of the population. Not all patients seek advice, especially within one family, resulting in marked underreporting. This drawback is compensated to some extent by the fact that the interpretation of data is commonly based on the incidence in one period as compared to another.

To what extent do the ILI-numbers as reported by the general practitioners, reflect the real extent of influenza morbidity? Some authors conclude that in general practice the distinction between influenza and influenza-like illness is reliable. At this point more research has to be done into the Dutch situation.

A disadvantage of a surveillance system based upon sentinel stations, despite the efforts made by the general practitioners, is the inertness. The ILI-figures are at the earliest available one and a half week after the collection. So the system can improve its effectiveness by computeri.

We believe that a good "direct" surveillance system based upon direct communication between general practitioners and the National Influenza Centre is an important tool in the prevention of the influenza related morbidity and mortality. This study indicates that the weekly number of influenza-like illness is a good prognostic parameter for the real impact of influenza. An electronic surveillance system could detect immediately the threshold after which the influenza mortality increases more than proportionally, at least if our model is valid. Reaching this level, electronic bulletins can stress the importance for prophylactic measures or, especially for the high-risk patient, the combination with amantadine or rimantadine to prevent excess mortality.
The benefits of such an electronic surveillance system are not restricted to the epidemic. We believe that such a system can improve the involvement of general practitioners in the surveillance of influenza and by this way improve the awareness of the consequences of influenza, possibly resulting in a higher degree of vaccination.

From chapter 4 it appeared that the overall mortality for 2 months (December 1989 and January 1990) rose 18%, the increase being most pronounced among those over 80 years old (26%). The number of excess deaths amounted to a total of 4100. In the two previous seasons (1988-1989 and 1987-1988) no excess deaths were registered by the Dutch Central Bureau of Statistics.
Thus, surprisingly in 1989-90 moderate morbidity is attended by high mortality, a phenomenon which could not be explained by a major antigenic drift, or by a lack of antibodies in the entire population.
Obviously the common methods to detect a drift or shift are not sufficient to explain this phenomenon. We suggest that the unusual increase in mortality rate is caused by a change in biological activity.
Unfortunately no figures were available of influenza mortality rate or other death causes, therefore it was not possible to use the regression model.

To summarize, on average more than 2000 people over 60 years are estimated to die related to influenza in The Netherlands per year. In future the influenza and influenza related mortality will gain in importance because the number of people over 60 years will increase to 25 per cent of the population in the USA in the year 2020.
A good "direct" surveillance system based upon direct communication between general practitioners and the National Influenza Centre is an important tool in the prevention of the influenza related morbidity and mortality. This could stimulate preventive measures like vaccination of the elderly.

Summary

The purpose of the first chapter was to assess the influence of influenza on the mortality from heart and lung diseases, in people over 70 years of age. With a regression model, the observed monthly mortality from heart and lung diseases in people over 70 years is explained with a yearly variable, a monthly variable, population size and the overall monthly number of influenza mortality cases, assuming that monthly mortality is generated by a Poisson process. The monthly excess mortality from heart and lung diseases due to influenza among elderly people (> 70 years) is estimated in the studied period 1967-1982.
This study suggests that per year 1,400 deaths were due to influenza per million people over 70 years of age, in the studied period of 16 years.
It can be concluded that 1 influenza death in the population above 70 years, "generates" almost 2 deaths diagnosed as heart and lung diseases in the elderly.

In chapter 2 the total impact of influenza will be estimated over a longer period (22.5 years). This means that the total population (all ages) and total mortality will be considered. At the outset death causes will firstly be divided into three main diagnostic categories:

1. heart disease
2. lung disease
3. other death causes

Two main categories are further subdivided, namely deaths due to heart diseases into five death causes and deaths due to lung diseases into two death causes. Also ages will be subdivided, namely into four age groups: 0-59 years, 60-69 years, 70-79 years and 80 years and over.
This study tries to attain five objectives:
1. Influenza-activity has been defined so far as the influenza mortality rate in the total population. A better indicator for influenza-activity might be influenza morbidity. In the first section three influenza-activity indicators and their combinations are compared with the object to choose the most effective (i.e. related) indicator for the new model.
2. In the second section the effect of a time-lag is considered. It is not unrealistic to assume that there is a time delay in the relationship between influenza activity and excess mortality; the effect on excess mortality might be observed about one month later than the influenza activity as its potential cause. Hence in the second section a model will be considered in which the influenza activity indicator has a time lag of one month.
3. Depending on the results obtained in sections 1 and 2 a tentative regression model will be fitted in section 3. On the basis of this model the influenza/excess mortality ratio will be estimated. This ratio represents the number of influenza related deaths for one registered influenza death. Influenza related mortality will be analyzed separately within each age group.

4. In section 4 influenza related mortality is examined within each diagnostic category, i.e. heart-, lung-, and other mortality categories within each age group.
5. In section 5 influenza related mortality will be considered separately for each subdivision of death causes within an age group. Heart mortality being subdivided into five death causes, and lung mortality into two death causes.
From the results it appeared that the influenza-activity parameter which gave the best fit of the model, is the influenza-mortality per month in the total population. No clear time-lag effect has been found which is taken as an indication that the major effect of influenza-activity on mortality for other causes does occur in the same month.
Our overall analysis indicated that one registered influenza death case is related with an overall 2.6 other death cases. This influenza related mortality occurs for 50% in the age group 60 - 79 and for the age group over 80 years 45% and only 5% in the age group under 60.
Almost half of the influenza related mortality is estimated to occur in the diagnostic group of heart diseases, about 25% in the group of lung diseases and about 30% in the remaining group of other mortality (not further defined).
In each diagnostic category (heart, lung and other) the age distribution is about the same with approximately 95% of the death cases in age group over 60 year.
Concerning the influenza related mortality in heart diseases the largest proportion occurs in the subgroup ischemic heart disease (44%), next, other heart diseases (30%) and third, cerebrovascular diseases (21%) whereas hypertensive heart disease and chronic rheumatic heart disease rank fourth (3%) and fifth (1%).
The proportion of influenza related mortality within subgroups by death cause is substantially the same. So the influenza related mortality is for example not associated with one particular heart disease.
In the diagnostic category of lung diseases the distribution of influenza related mortality in the subgroups by death cause, pneumonia and bronchitis/emphysema/asthma is fifty-fifty, when all ages are considered together. Within the two death cause subgroups the percentage influenza related mortality is the same in the various age groups.
During severe epidemics the proportion of influenza related mortality did reach a maximum level of 25%, i.e. a quarter of total mortality in all ages, in that particular month is related to influenza.

In the studied period (22.5 years) the average yearly direct mortality and related mortality for influenza turned out to be more than 2000 in people over 60 years in The Netherlands.

The purpose of chapter 3 is to investigate the relationship between the number of influenza-like illness (ILI), weekly registered by the general practitioners (sentinel-stations), and the monthly overall influenza-mortality, given by the Dutch Central Bureau of Statistics during the period July 1970 to June 1989.

The quantitative impact of influenza-morbidity is expressed by three summary parameters, deduced from the weekly ILI-figures, (i.) their sum (i.e. global extent of an epidemic), (ii.) their standard deviation, and (iii.) their maximum (i.e. peak number of ILI during an epidemic). These three parameters are mutually compared with respect to their predictability for total influenza mortality in the 19 season-years available.

No distinction is made between Influenza A and B or any subtype of influenza A, because no reliable figures of the incidence of each subtype are available.

In most cases, the standard deviation and the peak number of ILI are more powerful (efficacious) to predict the mortality, than the global extent of the epidemic.

Special interest has the peak number of ILI. This parameter is particularly useful to estimate the effect on the influenza- mortality already during an ongoing epidemic. As an implication of the model it is possible to calculate a threshold (of weekly ILI) beyond which mortality increases more than proportionally to the number of illnesses.
This study indicates that the weekly number of influenza-like illnesses is a certain prognostic value for the real impact of influenza. An electronic surveillance system could detect immediately the threshold after which the influenza mortality increases more than proportionally. Reaching this level, electronic bulletins can stress the importance for prophylactic measures or, especially for the high-risk patient, the combination with amantadine or rimantadine to prevent excess mortality.
The benefits of such an electronic surveillance system are not restricted to the epidemic. We believe that such a system can improve the involvement of general practitioners in the surveillance of influenza and by this way improve the awareness of the consequences of influenza, possibly resulting in a higher degree of vaccination.

In chapter 4 an observation about excess mortality is presented. The overall mortality for 2 months (December 1989 and January 1990) rose 18%, the increase being most pronounced among those over 80 years old (26%). The number of excess deaths amounted to a total of 4100.
Surprisingly this high mortality is attended by moderate morbidity in 1989-1990, a phenomenon which could not be explained by a major antigenic drift, or by a lack of antibodies in the entire population.

Samenvatting

De centrale vraag in dit gepresenteerde onderzoek is wat de werkelijke gevolgen van influenza zijn en of deze kunnen worden voorspeld.
Als er meer sterfte verband houdt met influenza dan in eerste instantie lijkt, is de volgende vraag bij wie deze "extra" sterfte optreedt.

Uit oudere studies, zelfs al in 1847, blijkt dat influenza meer sterfte kan veroorzaken dan alleen **direkt** aan influenza. Met andere woorden tijdens een influenza epidemie ziet men meer sterfte bij verschillende aandoeningen dan men op grond van het seizoen zou verwachten. Deze extra sterfte wordt aangeduid met de term "oversterfte".

In hoofdstuk 1 en 2 wordt een poging gedaan deze oversterfte te berekenen.

Door het Centraal Bureau voor de Statistiek (C.B.S.) worden de doodsoorzaken geregistreerd nadat door de arts de doodsoorzaak is vastgesteld. Door de arts wordt een zo nauwkeurig mogelijke overlijdens diagnose vastgesteld. Tijdens een influenza epidemie ziet men dan ook dat het aantal influenza sterfgevallen stijgt. Daarnaast ziet men ook een stijging van een aantal andere doodsoorzaken die in eerste instantie niets met influenza te maken hebben.

Met behulp van een zgn. regressie model wordt deze oversterfte geschat. In dat zgn. regressie model probeert men datgene waarin men geinteresseerd is, te schatten (voorspellen) aan de hand van een aantal gegevens.
Als de totale sterfte moet worden geschat zal het duidelijk zijn dat deze tijdens de winter altijd hoger is. Ook geldt voor een aantal sterfte oorzaken dat het voorkomen gedurende een langere periode is veranderd bv. door betere geneesmiddelen. Met al deze "verstorende" factoren moet rekening worden gehouden, maw. men moet hiervoor corrigeren.
In dit onderzoek is in eerste instantie getracht de totale sterfte te verklaren met behulp van vier gegevens. Ten eerste de maand van het jaar, ten tweede het jaar, ten derde de bevolkingsgrootte en als laatste de influenza-aktiviteit. Deze vier variabelen (ook wel correctie-factoren) moeten ervoor zorgen dat het model zo naukeurig mogelijk de sterfte schat. Het zal duidelijk zijn dat wij vooral in de influenza-aktiviteit geinteresseerd zijn.
Met behulp van een computer-programma wordt een wiskundig "model" gemaakt, dat de samenhang tussen aan de ene kant de vier eerder genoemde factoren en aan de andere kant de totale sterfte (of een andere waardè) aangeeft. Het rekenprogramma maakt een aantal wiskundige vergelijkingen en selecteert hieruit de best passende.

Het zal duidelijk zijn dat het model nooit perfect kan zijn, het blijft altijd een benadering van de werkelijkheid. Zelfs kan het mogelijk zijn dat er helemaal geen verband is tussen de te onderzoeken grootheden. Wel is het mogelijk de mate waarin het model kan schatten (de nauwkeurigheid) te bepalen, en zo te kunnen beslissen of het model "goed genoeg" is.
Nadat het model is vastgesteld en gecontroleerd kan men bepaalde gegevens veranderen waarmee een andere situatie wordt gesimuleerd. Een voorbeeld hiervan is het model van het Centraal Plan Bureau dat van de nationale economie een wiskundig model heeft gemaakt. Hierdoor kunnen ze b.v. de gevolgen van verschillende olieprijzen voor de economie berekenen.

In ons geval wordt over een lange periode (22,5 jaar) de totale sterfte geschat, rekening houdend met o.a. influenza. Door vervolgens te veronderstellen dat er geen influenza zou zijn geweest gedurende deze periode zal, indien influenza extra sterfte tot gevolg heeft, de totale sterfte lager worden geschat. Het verschil tussen de totale (geschatte) sterfte in een situatie van wel en geen influenza wordt de oversterfte genoemd.

Met behulp van een dergelijk regressie model worden bepaalde relaties gelegd. In de statistiek is het zeer moeilijk bepaalde oorzaken en gevolgen te "bewijzen". Ook in dit geval gelden alle uitkomsten niet als een "bewijs" dat influenza oversterfte veroorzaakt maar geldt het als zeer aannemelijk.

Als wordt getracht een relatie aan te tonen tussen influenza-aktiviteit en andere sterfte kan men deze influenza-aktiviteit op verschillende manieren vaststellen. Er kan worden gekeken naar het aantal influenza ziekte gevallen, naar de influenza sterfte of naar een combinatie van beide. Uit de analyse blijkt dat de beste maat voor influenza-aktiviteit de maandelijkse sterfte opgegeven door het C.B.S. is.

Het is mogelijk dat het effect van influenza pas later zichtbaar wordt in de totale sterfte. In de studie is een effect van 1 maand onderzocht. Uit de resultaten bleek dat de sterfte zich voornamelijk voordoet in dezelfde maand als waarin de influenza sterfte plaats vindt.

Het model wordt nu gebouwd met als maat voor de influenza-aktiviteit de influenza sterfte in diezelfde maand. Allereerst is getracht deze oversterfte in een eenvoudig model te verklaren.

De analyse laat zien dat indien een influenza sterfgeval wordt geregistreerd dit gerelateerd is aan nog eens 2,6 andere sterfgevallen. Deze oversterfte vindt voor 50% plaats in de leeftijdsgroep 60 - 79 jaar, voor 45% bij personen boven de 80 jaar en 5% bij personen jonger dan 60 jaar.

In de nadere analyse worden drie groepen onderscheiden: hartziekten, longziekten en de groep "alle andere sterfte" (wordt verder aangeduid met "andere sterfte").

Vervolgens wordt getracht zo nauwkeurig mogelijk te bepalen welke doodsoorzaken te maken hebben met deze oversterfte.
Ongeveer 50% van de oversterfte vindt plaats onder de noemer hartziekten, 25% longziekten en 30% niet nader gespecificeerd. Uit de analyse per leeftijdsgroep blijkt dat deze verdeling globaal voor iedere groep geldt; 95% boven de 60 jaar.

De groep hartziekten wordt vervolgens onderverdeeld in vijf subgroepen, de longziekten in twee subgroepen. De analyse wordt voor deze subgroepen per leeftijdsklasse opnieuw uitgevoerd (leeftijdsgroepen: 0-59j, 60-69j, 70-79j en boven 80 jaar).

Nagegaan wordt hoe de verdeling van oversterfte is over de vijf subgroepen van hartziekten. Binnen de groep hartziekten blijkt de oversterfte voor het grootste deel voor te komen in de subgroep ischemische hartziekten (o.a. hart-infarct) te weten 44%, vervolgens 30% binnen de subgroep "andere hartziekten" (niet nader aangeduid), 21% cerebrovasculaire ziekten (hersenbloeding) en 3% bij de hypertensieve hartziekten en ten slotte 1% bij de chronisch rheumatische hartziekten (o.a. hartklep afwijkingen).

Vervolgens wordt nagegaan hoe groot het aandeel aan influenza gerelateerde sterfgevallen is binnen iedere subgroep. Het blijkt dat deze verdeling globaal hetzelfde is. Dit betekent dat niet een bepaalde groep hartziekten sterk geassocieerd is met influenza sterfte.

Binnen de groep longziekten wordt een tweedeling gemaakt: pneumonie en de subgroep bronchitis/emfyseem/astma. Hier blijkt dat de verdeling van influenza gerelateerde sterfte ongeveer gelijk verdeeld is over de twee subgroepen. Ook het aandeel van influenza sterfte binnen de groepen is hetzelfde.

Tijdens ernstige influenza epidemieen kan van de totale maand-sterfte een kwart gerelateerd zijn aan influenza.

Het gemiddeld aantal influenza en aan influenza gerelateerde sterfgevallen gedroeg in de bestudeerde periode meer dan 2000 per jaar bij personen ouder dan 60 jaar in Nederland.

Vaak wordt geopperd dat de koude winter periode gepaard gaat met verhoogde sterfte, of er nu wel of geen influenza is. Dit is uiteraard juist maar hiermee is gedeeltelijk rekening gehouden door correctie-factor "maand" te gebruiken. De winter maanden, waarvoor gecorrigeerd is gaan (bijna) altijd gepaard met koud weer. Daarbuiten is het zeer moeilijk een eenduidige correctie factor voor het weer te vinden.

In de winter perioden zijn ook andere luchtweg virussen actief. Deze virussen leiden meestal niet tot ernstige complicaties, behoudens bij bepaalde risico patienten en kinderen. Verder veroorzaken deze virussen ieder jaar een epidemische verheffing. Ook voor dit verschijnsel is gecorrigeerd middels de maandfactor.

Vaak wordt gedacht dat de personen die dood gaan in relatie met influenza, ouderen zijn die toch al verzwakt waren, en binnen korte tijd zouden te komen overlijden. Uit deze studie en vele andere studies blijkt dat dit niet zo is, het leven wordt niet slechts met enkele maanden verkort.

De waarneming dat veel influenza gerelateerde sterfgevallen onder de noemer van hart- of longziekten worden gebracht kan te maken hebben met het feit dat artsen bij voorkeur de onderliggende ziekte als doodsoorzaak willen aanmerken.

Het regressie model kan uiteraard niet alles precies verklaren. Er blijft altijd een stuk onverklaarde variatie over. Indien deze onverklaarde variatie te groot is kan het zijn dat er een andere onderliggende factor een rol speelt. In dit verband is het belangrijk dat er geen systematiek te ontdekken mag zijn in de onverklaarde variatie. Uit een analyse hiervan blijkt dit niet het geval te zijn.

In deze studie zou het wenselijk geweest kunnen zijn, de preciese samenstelling van het influenza-virus dat de epidemie veroorzaakte, te kennen. Dit is echter niet mogelijk omdat vaak meerdere soorten influenza virussen een rol spelen tijdens een epidemie en er regionale verschillen kunnen optreden.

De vraag dringt zich op of het influenza-virus hartziekten veroorzaakt. Tot nu toe is er geen duidelijk bewijs geleverd dat dit met het influenza virus het geval is. Met betrekking hierop zijn twee dingen van belang. Ten eerste treedt de oversterfte uitsluitend op tijdens een influenza-epidemie, die vaak van korte duur is. Als men het influenza virus bij een hartziekte wilt vinden moet men precies tijdens deze epidemie zoeken. De gepubliceerde studies hebben voor het merendeel onderzoek gedaan tijdens de hele winter-periode zonder speciaal te kijken of er wel of geen influenza-epidemie was.
Ten tweede blijkt uit dit onderzoek dat de influenza gerelateerde sterfte niet aan een speciale hart doodsoorzaak is gebonden. De sterfte is relatief gezien over alle doodsoorzaken gelijk verdeeld. De vraag is echter hoe betrouwbaar de registratie is van doodsoorzaken bij hartziekten.
Als er toch een relatie blijkt te zijn tussen influenza en hartziekten is de vraag hoe deze biologisch kan worden verklaard.
Op dit gebied zal meer onderzoek dienen te worden gedaan. Met behulp van moleculair biologische technieken kan onderzoek worden gedaan dat dan mogelijk een nieuw licht op deze vraag werpt. Hierbij staat met name de vraag centraal of het virus of genetisch materiaal hiervan buiten de luchtwegen kan worden aangetroffen.

Waarschijnlijk zijn de schattingen in deze studie aan de lage kant. In de analyse is namelijk geen rekening gehouden met het feit dat een aantal ouderen en met name risico-patienten jaarlijks tegen influenza gevaccineerd worden en hierdoor minder kans op complicaties lopen. Indien dit niet het geval zou zijn, is de verwachting dat het aantal influenza gerelateerde sterfgevallen hoger zou uitvallen.

In hoofdstuk drie wordt getracht een model te maken dat het verband tussen influenza-sterfte en influenza-ziekte verklaard.
De vraag die centraal staat is of het mogelijk is m.b.v. de influenza-ziekte cijfers een voorspelling te geven over de te verwachten sterfte. De ziektecijfers worden gedurende de winter iedere week verzameld door de huisartsen van de peilstations van het NIVEL. Uit dit onderzoek blijkt dat de hoogte van een ziekte-piek een betere voorspellende waarde heeft op de sterfte dan het totaal aantal ziekte gevallen gedurende de hele epidemie. Een nog iets betere maat is de standaard deviatie van de ziekte cijfers. Een nadeel hiervan is echter dat deze pas na afloop van de epidemie kan worden vastgesteld. Dit geldt uiteraard ook voor het totaal aantal ziekte gevallen gedurende de epidemie.

Vervolgens was de vraag of iedere ziekte-piek met relatief dezelfde sterfte gepaard ging. Door het gebruikte wiskundige model bleek dat er een zgn. drempel waarde te berekenen was. Indien de piek deze drempel waarde overschrijdt, zal de sterfte relatief meer toenemen. Minstens twee verklaringen zijn hiervoor mogelijk. Ten eerste, hoge influenza ziekte leidt tot relatief hoge sterfte omdat het virus zich niet alleen snel verspreidt maar ook meer virulent (kwaadaardiger) is. Ten tweede, meer waarschijnlijke, als er veel influenza-aktiviteit is, is de kans op onderrapportage groot. Het is aannemelijk dat als een lid van de familie de arts bezoekt wegens griep, de andere leden van de familie dit niet opnieuw doen, indien ze ook griep krijgen, hetgeen tot onderrapportage leidt.
Indien de ziekte piek de geschatte drempel van 32 influenza-achtige ziektegevallen per 10.000 inwoners overschrijdt zal de sterfte relatief meer toenemen.
Het zal duidelijk zijn dat geen enkel systeem van gegevens verzameling m.b.t. infectie ziekten perfect is. Een reden hiervoor bij influenza ligt zeker in het feit dat ieder subtype van het influenza virus zijn eigen sterfte en ziekte patroon kan hebben. Het model zal waarschijnlijk kunnen worden verbeterd door met het subtype rekening te houden. In deze studie was dit niet mogelijk omdat er geen kwantitatieve gegevens beschikbaar zijn over subtypen.

Een ander nadeel van gegevens verzameling is de al eerder gesignaleerde onderrapportage. Toch is dit nadeel betrekkelijk omdat meestal vergelijkingen worden getrokken tussen de verschillende perioden.

De vraag kan worden gesteld of door de huisartsen de als influenza-achtige ziektebeelden ook daadwerkelijk door influenza worden veroorzaakt. Op dit punt dient nader onderzoek te worden gedaan. Wel kan worden opgemerkt dat influenza zich vooral voordoet in epidemieen. De kans dat een influenza-achtig ziektebeeld tijdens een epidemie door het influenza virus wordt veroorzaakt is hoog.

Een nadeel van de huidige peilstations is, ondanks alle moeite door de huisartsen en andere betrokkenen, dat de cijfers pas relatief laat beschikbaar komen, gemiddeld 1,5 week na afsluiting van de registratie week. Dit systeem kan worden verbeterd door een electronisch netwerk op te richten met als doel het registreren van infectie ziekten, i.h.b. influenza. Hierdoor kan de communicatie tussen de huisarts en het Nationaal Influenza Centrum worden verbeterd. Deze studie laat zien dat de ziekte piek een belangrijke indicator voor de gevolgen van influenza is. Een implicatie van deze indicator is dat bij ieder ziekte cijfer een minimum schatting van de gevolgen van influenza kan worden gemaakt.
Door snelle detectie van de ziekte en met name de drempel waarde, kunnen de huis- en verpleeghuis artsen in een vroeg stadium, via telecommunicatie, extra gewezen worden op de gevolgen van influenza. Hierdoor kunnen ze nog niet eerder gevaccineerde patienten alsnog vaccineren of risico patienten beschermen met Amantadine.

Het voordeel van een dergelijk electronisch surveillance systeem is niet alleen beperkt tot de epidemie. Wij geloven dat een dergelijk systeem ook de betrokkenheid van artsen bij de surveillance kan vergroten, en zo het bewust maken van de gevolgen van influenza. Mogelijk dat hierdoor de vaccinatie graad bij ouderen kan worden verhoogd.

In hoofdstuk vier wordt duidelijk dat de algemene sterfte in Nederland gedurende twee maanden (december 1989 en januari 1990) is gestegen met 18%, voor het merendeel bij ouderen boven 80 jaar. Het totaal aantal extra sterftegevallen is door het C.B.S. becijferd op 4100 personen. Volgens het C.B.S. was in de voorgaande jaren geen extra sterfte waargenomen. Het C.B.S. brengt deze stijging in verband met de afgelopen influenza epidemie.

Dit fenomeen kan niet worden verklaard door een verandering van het influenza virus of een tekort aan afweertoffen bij de bevolking.
Blijkbaar zijn de huidige methoden ter detectie van een virus verandering niet voldoende om een dergelijk fenomeen te verklaren, terwijl dit naar alle waarschijnlijkheid toch moet zijn veroorzaakt door een biologische verandering van het virus.

Jammer genoeg waren er nog geen cijfers beschikbaar over de doodsoorzaken waardoor het niet mogelijk was het regressie model toe te passen.

Samenvattend kan worden gesteld dat in Nederland gemiddeld per jaar meer dan 2000 personen boven de 60 jaar overlijden in samenhang met influenza.
In de toekomst zal dit belangrijker worden gezien de toenemende vergrijzing in Nederland.
Wij geloven dat een goed "direkt" surveillance systeem, gebaseerd op direkte communicatie tussen huisartsen en het Nationaal Influenza Centrum een belangrijke rol kan spelen bij de preventie van deze influenza gerelateerde sterfte. Mogelijk dat een dergelijk systeem de vaccinatie-graad bij ouderen kan bevorderen.

Dankwoord

Aan mijn ouders ben ik grote dank verschuldigd. Zij hebben mij op jeugdiger leeftijd vaak bij de les moeten houden ook als het niet mijn interesse had.

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Ten slotte prof. dr. N. Masurel. Sinds 1985 is hij mijn "begeleidend leermeester". Sinds 1988 hebben we bijna dagelijks overleg gevoerd over dit onderzoek, hetgeen tot grote vreugde en vriendschap heeft geleid. Nog jaren hoop ik gebruik te mogen maken van zijn genegenheid en kennis; hij **is** de **influloog**!

En dan Myriam, mijn vrouw, die dit alles heeft moeten doorstaan, met liefde en geduld.

Curriculum Vitae

De auteur van dit proefschrift werd 30 juli 1962 geboren te Maastricht.
Hij bezocht het Stedelijk Lyceum te Maastricht waar hij het Atheneum diploma behaalde.

In 1982 begon hij de studie geneeskunde aan de Rijksuniversiteit Limburg te Maastricht. Deze universiteit had een andere onderwijs filosofie, de nadruk werd gelegd op het aanleren en of vergroten van het probleemoplossend vermogen. Middels casus gericht onderwijs heeft hij het doctoraal diploma behaald in 1986 en na het doorlopen van de co-assistentschappen het arts-examen in 1988.

Tijdens zijn studie is hij in kontakt gekomen met de vakgroep economie van de gezondheidszorg (hoofd prof. dr. F.F.H. Rutten). De kwantitatieve benadering van gezondheidszorg problemen sprak erg aan. Door het onderzoek met betrekking tot economische evaluatie van vaccinatie is hij via een verzoek van drs. J. de Waard (Regionaal Ziekenfonds Twente) in kontakt gekomen met prof. dr. N. Masurel van het Nationaal Influenza Centrum van de Erasmus Universiteit.

In 1985 is een begin gemaakt met het onderzoek dat mede door de stimulerende werking van prof. dr. N. Masurel tot deze dissertatie heeft geleid.

In 1988 werd aangevangen met de opleiding tot medisch microbioloog (virologie) in het academisch ziekenhuis Dijkzigt en Sophia kinderziekenhuis te Rotterdam (opleiders prof. dr. N. Masurel, virologie en prof. dr. M. Michel, bacteriologie).
Sinds 1990 is hij tevens aan de Erasmus Universiteit te Rotterdam verbonden als universitair docent in de virologie.