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Influenza mortality and excess deaths in the elderly, 1967–82

M. J. W. SPRENGER[1], M. A. M. G. VAN NAELTEN[2], P. G. H. MULDER[3] AND N. MASUREL[1]

[1] *Department of Virology and WHO Influenza Centre, Erasmus University Rotterdam, Rotterdam,* [2] *Department of Regional Planning, Faculty of Policy Sciences, Catholic University of Nijmegen, Nijmegen,* [3] *Institute of Epidemiology and Biostatistics, Erasmus University Rotterdam, Rotterdam, The Netherlands*

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SUMMARY

This study assessed the influence of influenza on mortality from heart and lung diseases in people over 70 years of age. The data used were obtained from the Dutch Bureau of Statistics. With a regression model, the observed monthly mortality from heart and lung diseases (influenza not included) in people over 70 years is explained with a yearly variable, a monthly variable and the overall monthly number of influenza mortality cases, assuming that monthly mortality has a Poisson distribution. The monthly excess mortality from heart and lung diseases (influenza not included) due to influenza among elderly people (> 70 years) is estimated.

This study suggests that 1400 deaths per million per year were due to influenza in people over 70 years of age in the study period of 16 years.

It can be concluded that one influenza death in the population over 70 years 'generates' almost two deaths diagnosed as heart and lung diseases in the elderly.

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 & 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 inlfuenza 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.

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

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

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).

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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

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 of 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 assuming that influenza activity is nil. In

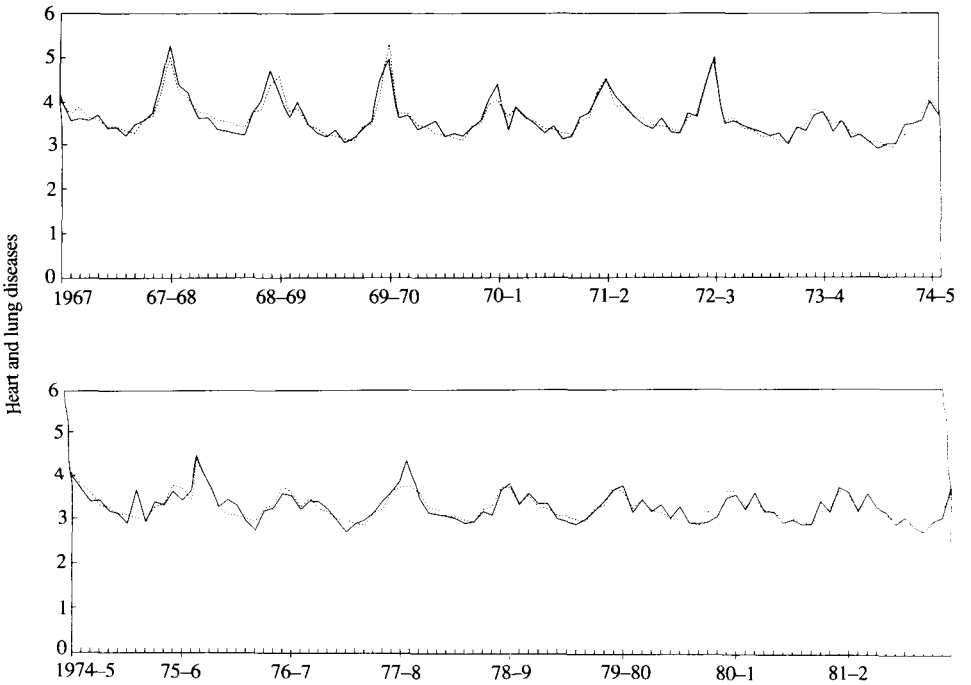

Fig. 1. Monthly observed mortality and predicted mortality (influenza deaths not included) from HDCLD per 1000 persons > 70 years in The Netherlands. ———, Observed mortality from HDCLD; ------, predicted mortality from HDCLD.

Table 2. *Estimated number of deaths HDCLD per thousand in people over 70 years and 95% confidence limits, using a Poisson regression analysis with 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
September	3·241	3.195	3·287
October	3·564	3·514	3·613
November	3·636	3·586	3·686
December	4·099	5·166	5·522
Influenza rate	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.

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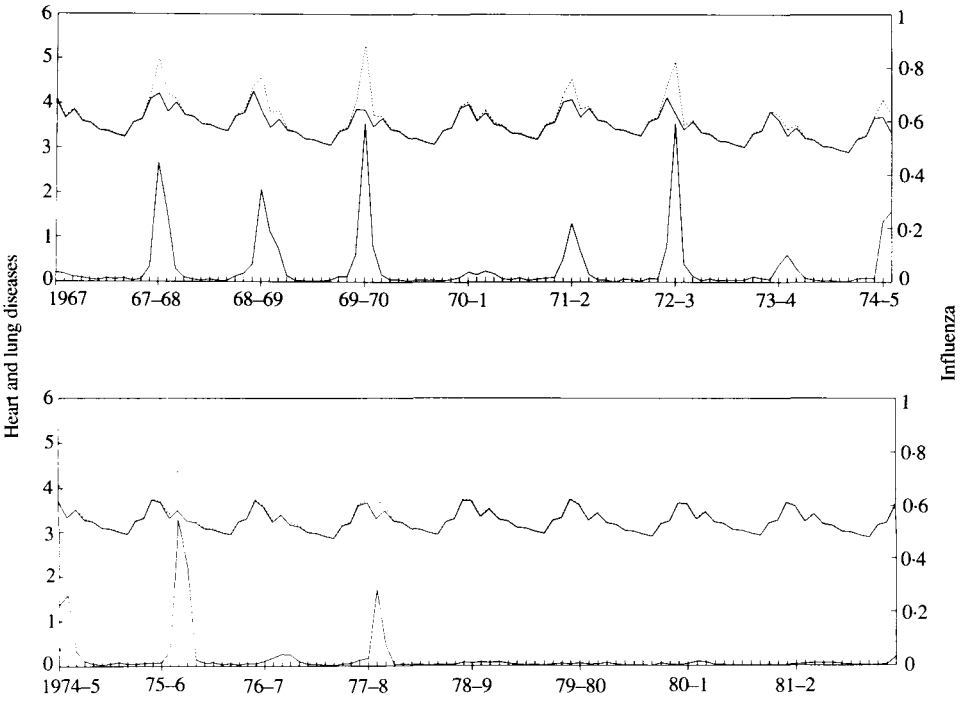

Fig. 2. Monthly predicted mortality (influenza deaths not included) with and without the explanatory effect of influenza mortality per 1000 persons > 70 years in The Netherlands. Baseline: influenza mortality. ------, Predicted mortality from HDCLD with influenza activity; ———, predicted mortality from HDCLD without influenza activity.

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 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 β coefficients) are not listed in Table 2.

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 (1967–8) 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

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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*	Influenza deaths*	Influenza-associated deaths†	Viral strains at large
1967–8	46140	898	2376	A/Asian/(H2N2)
1968–9	43954	827	2388	A/HK/(H3N2)
1969–70	43366	929	3046	A/HK/(H3N2)
1970–1	42518	206	525	A/HK/(H3N2)
1971–2	44132	529	1496	A/HK/(H3N2)
1972–3	43890	886	2526	A/Eng/(H3N2)
1973–4	39698	307	780	A/PortC/(H3N2)
1974–5	40053	621	1645	A/PortC/(H3N2)
1975–6	41752	1083	2761	A/Vict/(H3N2)
1976–7	38730	206	522	A/Vict/(H3N2)
1977–8	39801	454	1157	A/Tx/(H3N2) A/USSR/(H1N1)
1978–9	39347	91	234	A/Tx/(H3N2) A/USSR/(H1N1)
1979–80	39240	63	157	A/Bank/(H3N2)
1980–1	38517	65	166	A/Tx/(H3N2) A/Bank/(H3N2)
1981–2	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 years, with HDCLD estimated from the model.

in the middle of 1968 circulated in Europe unchanged for four successive winters causing variable amounts of damage (13). The first (1968–9) and second (1969–70) outbreaks were associated with high morbidity and mortality. The third period (1970–1) gave little mortality and the last (1971–2) 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 1968–71.

In the winter of 1972–3 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 1975/6 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 1977–8. 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 instead 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 syncyhal 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 illnesses. 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 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 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 1972–3 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 a 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 1968–76.

Influenza has a larger impact on mortality than just those cases who 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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