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Estimating influenza-related hospitalization in the Netherlands

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SUMMARY

The purpose of this study was to examine the impact of influenza on hospitalization in the Netherlands. Two methods were applied to estimate this effect: (a) regression analysis and (b) comparison of hospitalization in epidemic years with non-epidemic years. Hospital discharge rates in 1984 – 93 have been considered. The study shows that, during the period studied, on average, almost 2700 people were hospitalized for influenza per annum, and that influenza was diagnosed as the main cause for hospitalization in only a fraction of these hospitalizations (326: 12%). From an economic perspective, these results imply that the cost-effectiveness of vaccination against influenza may be severely underestimated when looking only at changes achieved in the number of hospitalizations attributed to influenza.

INTRODUCTION

Morbidity and mortality associated with influenza have long been recognized [1–4]. The total impact of influenza encompasses not only primary (direct) morbidity and mortality but also excess (indirect) morbidity and mortality. In 1848 Farr 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, an epidemic occurred [1].

Internationally, two methodological approaches have been applied to estimate excess morbidity and excess mortality associated with influenza. The most common, the comparative approach, compares morbidity in epidemic years with that in non-epidemic years, and defines excess morbidity as the difference between those [2, 4–6]. For example, in the state of Oregon, US, for some diseases, up to 50% more hospitalizations were found in epidemic years compared with non-epidemic years [5].

Other studies have sought to explain influenza-related mortality or morbidity by regression analyses. In 1963, Serfling derived a regression function to describe normal seasonal variations in mortality as well as time trends over the longer term [7]. This function and its several subsequent modifications have provided the basis for estimating excess mortality since used by, among others, the WHO [8]. For the UK, Clifford and colleagues [9] estimated excess morbidity using regression analysis and found that the 1969/70 outbreak was associated with 1·5 million excess claims for sickness. Comparable research on excess mortality in the Netherlands found that in the period 1967–89, on average, more than 2000 people

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died from influenza in the Netherlands annually. However, influenza was recognized as the primary cause of death in only a fraction (565: 27%) of these deaths [10, 11].

The mutual application of the two approaches has not been performed before in a single study, although it allows insight into the adequacy of the respective approaches to estimate excess morbidity or excess mortality. Moreover, it provides a solid basis for interpreting the results. In this paper, both approaches are applied to estimate excess hospitalization in the Netherlands. The hypothesis is that some hospitalizations which are attributed on hospital discharge certificates to diseases like pneumonia or chronic heart disease, are in fact caused by influenza. In both approaches, excess hospitalization is estimated by determining the influenza-related share of monthly hospitalizations for some specific diseases. In the regression analyses, models are developed to estimate hospitalization for these diseases in accordance with hospitalization observed in the period 1984–94. The models consist of variables that describe long-term trends, monthly patterns and influenza activity. Based on the impact of the latter, the number of hospitalizations linked to influenza, but attributed to other diseases, can be estimated. In the comparative approach, excess hospitalization is estimated by comparing annual hospitalizations for the diseases in the period 1984–94 with those during a year of low influenza activity, 1986–7. Observed differences are considered as excess hospitalization.

From an economic perspective, excess hospitalization may have a large impact on the cost-effectiveness of vaccination against influenza. If only the changes in hospitalizations attributed to influenza are considered, the economic attractiveness of vaccination may be seriously underestimated. The results of the present study apply to the economic evaluation of influenza vaccination reported elsewhere [12].

METHODS

The question of which share of the total number of hospitalizations in the Netherlands can be attributed to influenza is central to the analyses. In other studies, a number of diseases have been identified as important contributors to influenza-related excess morbidity and excess mortality [2–6, 9–11]. These include pneumonia (ICD-9 codes 480–486), cerebral-vascular accident (CVA, ICD-9 codes 430–438), chronic heart disease (CHD, ICD-9 codes 410–414), and diabetes mellitus (DM, ICD-9 code 250). The monthly number of hospital discharges for all these diseases, as well as for influenza (ICD-9 code 487), have been obtained for the period January 1984–December 1994. The data was collected and provided by the National Hospital Administration (SIG) which includes 99% of all hospital discharges in the Netherlands between 1984 and 1994 [13, 14].

Data concerning hospital discharges have been selected as these more accurately reflect patients' diseases than do hospital admission diagnoses. However, the admission dates of all hospital discharges related to the diseases mentioned are required to consider adequately the relation between influenza activity and hospitalization. These are determined by considering the respective hospital discharge dates and the respective lengths of hospital stay. For a detailed analysis, and to allow comparisons with research on excess mortality in the Netherlands [10, 11], these hospitalization data are obtained age-specifically. Four age groups are distinguished: 0–59 years, 60–69 years, 70–79 years, and 80 years and older. In the analyses, influenza years are defined from July through June of the following year as this reflects the natural course of influenza epidemics.

For illustrative purposes, Figure 1 shows influenza activity defined as the monthly number of hospital discharges for influenza (all diagnoses, all ages, as allocated to the month of hospital admission) between 1984 and 1994. On average, annually 326 persons were hospitalized with influenza diagnosed as the primary cause for hospitalization. [Note: For some age-groups and diseases, December 1988 and December 1992 values are not available due to data collection problems: in those cases values are determined by interpolation. Furthermore, the presence of specialist strikes in the influenza year 1987–8 has most likely influenced hospitalization data. For this reason, this year is not considered in the definition of reference year in the regression analyses and the comparative analyses.]

Regression analysis

Regression analysis applies the technique of modelling to determine the part of the total number of hospitalizations for specific diseases that can be explained by influenza. A number of models, specific to the diseases under scrutiny and to the age groups, are constructed. Every model is based on data from January 1984 to December 1994. In every model, the

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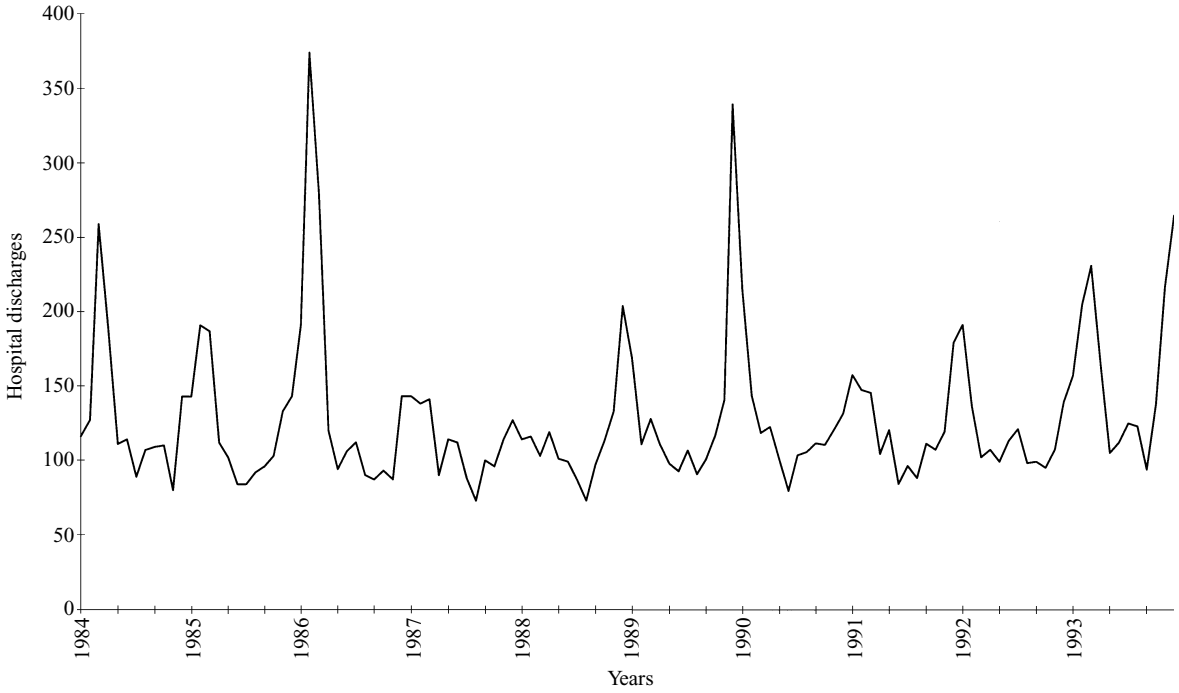

Fig. 1. Hospitalization for influenza (all diagnoses). Source: hospital discharge data 1984–93 (13).

monthly number of observed hospitalizations is explained by regressor variables that describe long-term trends (year variable), monthly patterns (month variable) and influenza activity (influenza indicator). Models account for long-term trends and monthly patterns to control for factors that are causally and temporally related to hospitalization for the diseases under study but that are not linked to influenza. For example, any structural impact of temperture changes on hospitalizations is accounted for by including the month variable. Specific background information on these variables and the model in general is given in the Appendix.

A model assigns values to the parameters included; the value γ that is addressed to the variable that represents monthly influenza activity is of particular interest. This value, which is specific to disease and age group, refers to the impact of influenza on the estimated hospitalizations during the period under study, 1984–94. This impact in terms of hospitalizations is further estimated by a two-step approach. First, the effect of influenza is eliminated by setting the influenza activity in the model at zero, while keeping the effects of year and month the same. The model predicts in that event the number of hospitalizations if no influenza had taken place. Next, the difference between predicted hospitalization in the situation of observed influenza activity and predicted hospitalization in the absence of influenza activity is considered. This difference is defined as the excess hospitalization associated with influenza (specific to disease and age group).

Various alternative models are defined. A number of alternative influenza indicators, that ideally should be sensitive and specific to influenza outbreaks, have been applied. These are: hospitalization for influenza, primary diagnoses; hospitalization for influenza, all diagnoses; hospital mortality due to influenza, primary diagnoses; hospital mortality due to influenza, all diagnoses. Furthermore, it is recognized in the model that hospitalizations for the diseases under scrutiny may react with a delay of 1 or 2 months following an outbreak of influenza. With this in mind, in addition to analyses ignoring the issue of time-lags, alternative analyses have been carried out including time-lags of 1 month and 2 months.

Variables are considered significant in the model when they are at least at the 5% level. The selection of alternative models (e.g. with or without time lag) is based on their explanatory power. This is indicated by R^2, which refers to the proportion of variance in the dependent variable accounted for by the model (for more details, see Appendix).

Comparative analysis

In comparative analysis, hospitalization for a number of diseases in periods with high influenza activity is

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Table 1. *Yearly excess hospitalization per 100000 by disease and age (years)**

	Regression analysis		
	Estimate	95% confidence interval	Comparative analysis†
Pneumonia			
0–59	3·0‡	(0·3, 5·1)	1·2
60–69	27·4‡	(21·5, 32·9)	7·1
70–79	81·8‡	(68·5, 92·7)	18·6
80 and older	220·2‡	(148·7, 272·4)	38·9
Cerebral-vascular accident			
0–59	−840·6	(−2222·3, 270·6)	471·3
60–69	−205·4	(−1109·9, 310·0)	−105·7
70–79	−204·9	(−1163·6, 832·3)	51·9
80 and older	2475·1	(−1802·0, 4802·4)	−131·5
Chronic heart disease			
0–59	−532·2	(−1050·4, 258·2)	−50·0
60–69	−303·2	(−833·7, 31·8)	65·8
70–79	237·7	(−314·4, 509·8)	74·2
80 and older	971·0	(−913·2, 2106·6)	18·1
Diabetes mellitus			
0–59	−14·4	(−207·8, 171·2)	99·4
60–69	42·9	(−235·1, 305·1)	167·2
70–79	74·2	(−311·9, 433·3)	126·5
80 and older	16022	(−1622·1, 3896·7)	116·0

* Denominator refers to the number of persons in the subgroup. For pneumonia, the denominator equals the total Dutch population [15]. For CVA, CHD, and DM, the denominator equals the number of patients with the respective disease [16].
† Since the reference case encompasses only one year, confidence intervals are not estimated.
‡ Significant at 5% significance level.

compared with that in (reference) periods with low influenza activity. The hypothesis is that any detected differences in hospitalizations can be attributed to influenza. To exclude differences in hospitalizations outside influenza outbreaks, the periods usually comprise 3–4 months enveloping influenza activity in a given year [2, 5].

In the present analysis, influenza activity is defined as hospitalization for influenza, all diagnoses. As a reference period, we selected 3 adjoining months that involve the lowest influenza activity between the months of November and April in the years 1984–94. This period, which simulates the near absence of influenza, is the period December 1986 to February 1987. Also, for each influenza year between 1984 and 1994, periods of three adjoining months are defined so that each period encompasses the highest influenza activity. Next, hospitalizations for the diseases under scrutiny in these periods are compared with those in the reference period. The difference between these hospitalizations indicates the excess hospitalization attributed to influenza in a given year. In the analyses, comparisons are specific to disease and age group.

This analysis focuses on differences in hospitalization for a number of diseases *between* years, and attributes these differences to influenza activity. However, any differences caused by other factors (e.g. the annual increase in hospitalizations for CHD because of changes in lifestyle) may bias the estimates. Therefore, preliminary to the principal calculations, the figures regarding hospital discharges were corrected by regression analysis for trends over the years.

RESULTS

Regression analyses

The variables describing long-term trends and monthly patterns were significant at a 5% level in all models. The results are less clear with respect to the variable

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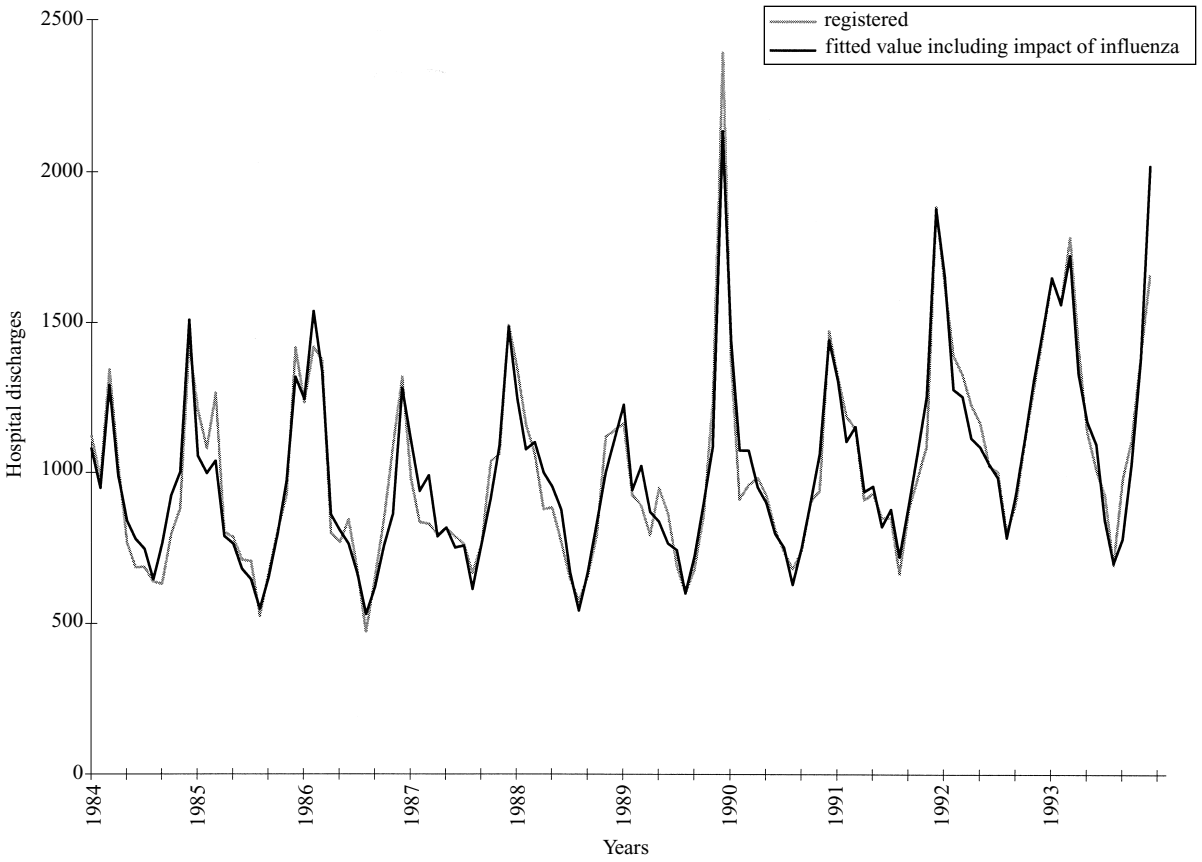

Fig. 2. Registered and predicted hospitalization for pneumonia, all age groups. Source: hospital discharge data 1984–93 (13) and as predicted by model.

that describes influenza activity. Disregarding its exact definition, this variable was significant only in the models on pneumonia (all age groups). The explanatory power of those models, as indicated by R^2, was best when the number of hospital discharges for influenza, all diagnoses, was selected as the influenza indicator. The inclusion of time-lags did not enhance the explanatory power of the models. The value of the influenza-indicator γ in the selected models on pneumonia regard from 0·0018 (S.E. 0·0008) to 0·0161 (S.E. 0·0032) for individuals in the age groups of respectively 0–59 years and 80 years and older.

Table 1, first column, presents the average annual number of excess hospitalizations per 100000 persons that can be attributed to influenza, derived from the regression analyses. This is estimated as the total number of excess hospitalizations divided by the number of years considered. As noted, significant excess hospitalization is only pertinent for the case of pneumonia (in absolute terms 2358 hospitalizations within a population of about 15 million people). Although there were some excess hospitalizations for CVA, CHD and DM, these are not significant. Therefore, excess hospitalization is not indicated for those diseases.

Based on these observations, further analysis is limited to pneumonia cases. Figure 2 shows that the predicted hospitalization for pneumonia matches the observed hospitalization fairly well. This implies that the model explains a large part of the variation in the monthly hospital discharge rates (which is also indicated by a high value of R^2: 0·88). The figure also shows that, in general, the pattern of the predicted hospitalization for pneumonia resembles that of influenza activity (as shown in Fig. 1).

Excess hospitalization is visualized in Figure 3 as the difference between predicted values including the impact of influenza, respectively assuming the absence of influenza. The figure shows that the pattern of excess hospitalization is very similar to that of influenza activity (as shown in Fig. 1), except for the year 1985/6. In this year, influenza activity reached its highest value in February, but the predicted hospitalizations for pneumonia shows no such large peak. This can be explained by the absence of peak values of influenza activity in February in other years which

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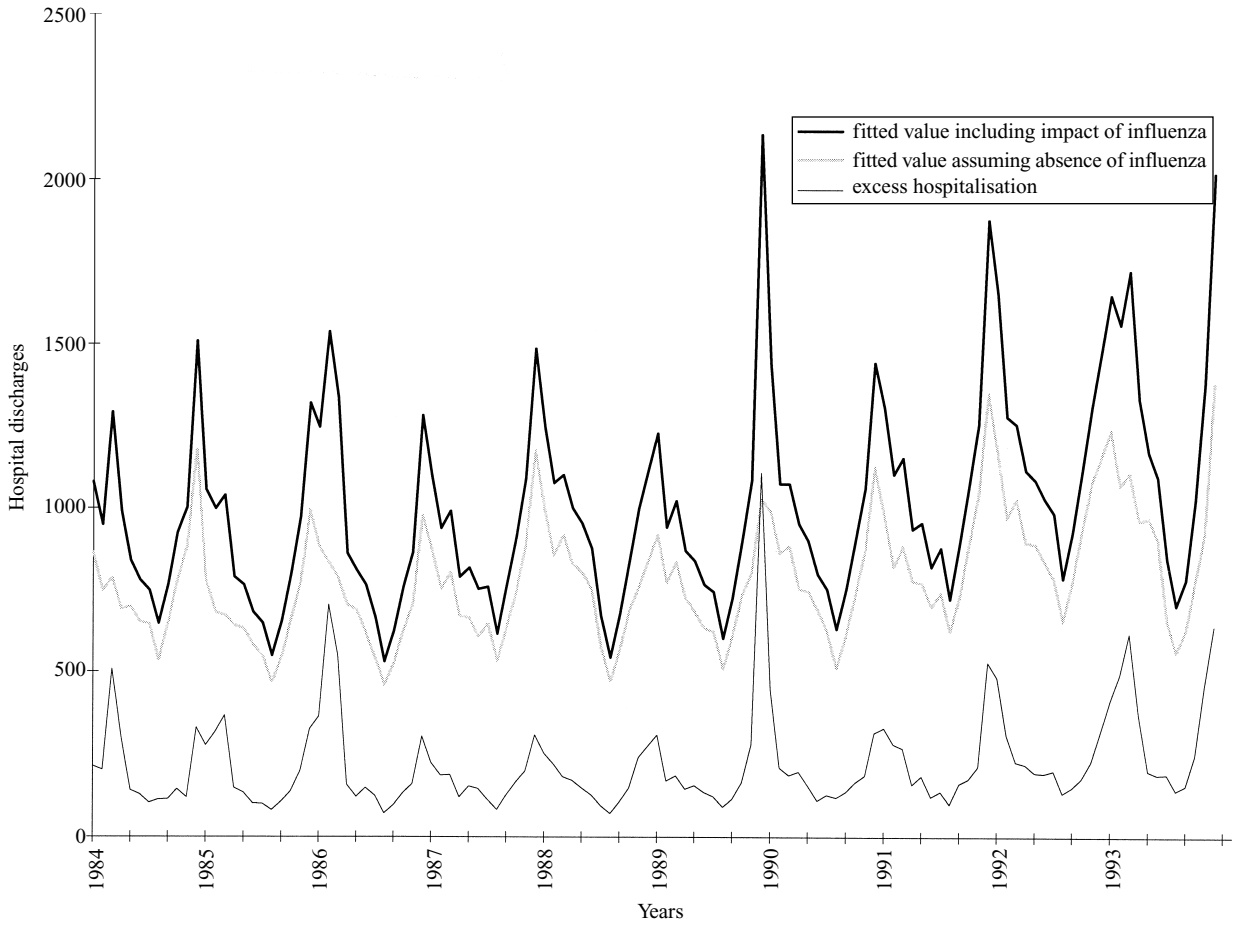

Fig. 3. (Excess) hospitalization for pneumonia, all age groups. Source: as predicted by model.

causes the model to assign a relatively low value to this month variable. Consequently, this has a decreasing effect on predicted hospitalizations in these February months. The presence of some excess hospitalization during summer seasons can be explained by the diagnoses of some cases of influenza during these seasons (as shown in Fig. 1).

Comparative analysis

As noted, regression analysis was carried out preliminary to the comparative analysis to correct for trends in the yearly number of hospitalizations that may bias the estimates. These analyses have been carried out on hospitalization data for all diseases and all are groups. Significant yearly trends regarding hospital discharges for all diseases and all age groups, except for CVA, were identified. These trends were corrected for with the most recent year, 1993/4, as base year.

The results of the comparative analyses are presented in the second column in Table 1. The table shows large numbers of excess hospitalizations for all age groups regarding pneumonia, and for most age groups regarding CHD and DM. For CVA, smaller and, for two out of four age groups, negative numbers of excess hospitalizations are found.

Excess hospitalization by risk groups and age

Policy-making regarding influenza vaccination is predominantly based on the classification of individuals according to age and risk status. A typical age distinction is between those below 65 years of age and those 65 years or older. Individuals are labelled as high-risk when they have one of the diseases that predispose for influenza or that aggravate the course of disease once infected. High-risk individuals are defined by the Health Council of the Netherlands as individuals having one or more chronic illnesses such

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Table 2. *Yearly excess hospitalization per 100000 by risk group and age (years)*

	Direct hospitalization*† (1)	Excess hospitalization†‡ (2)	Total hospitalization (3) = (1)+(2)
Low-risk			
0–64	0·1	0·3	0·4
65 and older	2	38	40
High risk			
0–64	28	72	100
65 and older	10	175	185

* Defined as the number of hospital discharges with influenza as the primary diagnosis.
† Allocation to high- and low-risk groups is based on US research [2]. For the age group 60–69 years, the average of the relevant figures regarding individuals younger than 65 years and those of 65 years and older is taken.
‡ Includes only *significant* numbers of excess hospitalization.

as IHD, CVA, DM, other heart diseases (ICD-9 codes 415–417) or bronchitis, emphysema and asthma (ICD-9 codes 490–493) [17]. The allocation of the numbers of excess hospitalizations to these subgroups of individuals is relevant in context of the feasibility of influenza vaccination. The economic attractiveness of vaccination may very well depend on the extent to which it can prevent (excess) hospitalizations.

For these reasons, the results of the present analysis are also classified according to these distinctions. The classifications are based on results from the regression analysis which, for reasons explained in the discussion section, is preferred to the comparative analysis. Only significant excess hospitalization is included. This implies that from the high-risk conditions mentioned above, no excess hospitalization estimated is allocated to high-risk groups. A large part of the excess hospitalization that is attributed to pneumonia should, however, be allocated to high-risk groups. From research in the US, it can be derived that, for individuls 65 years and older, 77% of all excess hospitalization for pneumonia occurs in high-risk patient-groups. Below the age of 65 years, 93% of all excess hospitalizations for pneumonia occurs in high-risk patients [2]. In the present analysis, these figures have been applied to allocate the excess hospitalization for pneumonia to high-risk and low-risk groups.

Table 2 presents the various hospitalization rates per 100000 individuals, as assigned to risk and age groups. The third column shows that the excess hospitalization for pneumonia, attributed to low-risk and high-risk groups, increases with age and is more important for high-risk compared to low-risk groups.

DISCUSSION

The present study indicates that, on average, almost 2700 people were hospitalized for influenza annually and that influenza was diagnosed as the main cause for hospitalization in only a fraction of these hospitalizations (326: 12%). This means that a large proportion (88%) of all influenza-related hospitalizations were not recognized as such. Excess hospitalization seems to be more relevant for the elderly than for the young and more pertinent in the high-risk population than in the low-risk population. All excess hospitalizations identified were hospitalization diagnosed as pneumonias.

The fact that a number of diseases are not included in the present analysis has most likely caused an underestimation of the magnitude of excess hospitalization. These diseases have been shown to account for about one-third of all influenza-associated deaths in the Netherlands [10, 11]. The impact of these diseases on excess hospitalization is unknown and will be topic of further research. Furthermore, during the period studied, only a few moderate outbreaks of influenza have occurred in contrast to the large number of more intense epidemics prior to this period (especially in 1971–8). The relative absence of large clusters of influenza activity in the present study makes detection of influenza-related hospitalization more difficult.

In this study, two approaches have been addressed to estimate the magnitude of excess hospitalization. For pneumonia, both the regression analysis and the comparative analysis yield (significant) excess hospitalization. For the other diseases, the results are less

clear. Nevertheless, the vast majority of all results stemming from the comparative analyses lie within the (in some cases very broad) 95% confidence interval as indicated by the regression analyses (although figures do not correspond for the youngest age groups). As we see it, regression analysis is preferable to comparative analysis for estimating excess hospitalization. In the regression approach, influenza activity is set to a level indicating the absence of influenza (keeping the effects of year and month the same). In contrast, in the comparative approach, the reference year is not likely to be entirely free of influenza activity; this may decrease observed hospitalization differences across diseases between this reference year and years with influenza activity. This may explain the relatively small numbers of excess hospitalization found in the comparative approach compared with those found in the regression approach. This also implies that, in the comparative approach, results are likely to be dependent on the choice of reference years(s) and they should be interpreted with caution. This is especially the case if comparisons are limited to only a few years. In this context, we decided not to report the results of an alternative comparison of 2 epidemic years with 1 reference year (compare (2)) due to the large sensitivity of the results in relation to the definition of the respective periods. Furthermore, while the main advantage of the comparative analysis seems its simplicity, regression analysis, as applied prior to the principal analysis, is still required to control for confounding trends over years.

Some issues should be considered critically when interpreting the results from regression analysis. It should be noted that excess mortality and excess morbidity are statistical concepts and cannot prove a causal relationship between influenza and non-registered influenza hospitalizations. Ideally the analysis should be carried out by distinguishing the different strains (H3N2, H1N1, B) that are mainly responsible for the different epidemics. This, however, is not feasible due to the lack of quantitative information on the causative subtype of influenza. However, the strong statistical correlation observed in the regression analysis suggests that the relation between influenza activity and non-registered hospitalizations is more than just a matter of coincidence. A number of plausible biological relationships further support this relation. Diabetes melitis patients are assumed to have an impaired immune response to the influenza virus [18] and are especially endangered by '*Staphylococcus aureus*' skin infection during influenza epidemics; this has previously been demonstrated to be a major risk factor in the development of secondary staphylococcal pneumonia [19]. Furthermore, it has been suggested that certain influenza strains increases platelets' stickiness, thus making the formation of platelet aggregates more likely and resulting in the possibility of precipitating ischaemic heart disease [20, 21]. Influenza has also been recognized as the most important viral infection of the respiratory tract, partly because of complications which have been shown to include exacerbations of pre-existing diseases as asthma [22, 23].

The presence of external factors may bias the results stemming from regression analyses. For example, monthly hospitalization rates may be influenced by external factors that limit the identification of excess hospitalization. For example, regarding hospitalization for CHD, we found structural decreases in hospital discharges in the months of December followed by increases in discharges in the months of January, possibly caused by the low number of working days in December or the reluctance of potential patients to be admitted to hospital during the December holidays. If structural, these differences across months are accounted for in the regression analysis by including a month variable. However, temporal events that are not caused by influenza but that do affect hospitalization may certainly bias the estimates. Ignoring such events may cause an incorrect estimation of the role of influenza in hospitalizations. For example, some excess hospitalization attributed to influenza may instead be caused by the respiratory syncytial (RS) virus. This virus, which also shows high activity during winter seasons, also causes respiratory infections like pneumonia. However, as the virus is mainly predominant in children, its confounding impact on this analysis will be limited.

Another important issue in regression analysis is the choice of hospital discharges, all diagnoses, as the indicator for influenza activity. Although this resulted in the best fit, it should be noted that it suggests the presence of influenza activity during summer months, which may partly be caused by over-diagnosing. This may result in an over-estimation of excess hospitalizations identified during these months.

In our analyses, as in other studies [9–11], it is assumed that the effect of influenza activity on hospitalization for a certain disease, as represented by γ, is constant over different time periods. From a theoretical point of view, the value of γ should be

period-specific to include changes in the prevailing types of influenza viruses. However, as noted, this is not feasible due to the lack of quantative information on the causative subtype of influenza. Moreover, differentiating periods would considerably diminish the number of observations to be used in each analysis and hence its power to produce significant results.

The results are in accordance with those found in other research. In studies on excess hospitalization in other countries as well, the vast majority of all identified excess hospitalizations were found to be cases registered as hospitalizations for pneumonias. In the state of Oregon, US, 8 years (up to 4 months) with influenza activity were compared to one reference year comprising a (near) absence of influenza. Regarding the high-risk population, more hospitalizations were found for pneumonia and influenza (up to 50%) for all epidemic years considered [6]. Another study in the state of Oregon found that hospitalization for pneumonia and influenza in 2 epidemic years exceeded that in a (non-epidemic) reference year by 140–150%. Excess hospitalization for acute cardiac failure and acute respiratory diseases other than pneumonia could not be proven [2]. In the Netherlands hospitalizations of diabetes mellitus patients because of pneumonia in epidemic years were found to exceed those in non-epidemic years by 45–300% [24].

Research on excess mortality in the Netherlands found that the identified excess deaths were deaths registered as due to various disease categories like CHD (34%), COPD (17%) and other diseases (22%) [10, 11]. This indicates that the nature of hospital discharges data is different from that of mortality data. During periods of influenza activity, influenza-related hospitalizations seem to be classified relatively often as pneumonias, while influenza-related deaths may more often be certified as due to a wider range of diseases.

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APPENDIX

The analyses have been carried out by using the procedure GENMOD of the statistical package SAS 6.03 [25]. The GENMOD procedure fits generalized linear models [26]. The class of generalized linear models is an extension of traditional linear models which allows the mean of a population to depend on a linear predictor through a non-linear link function and allows the response probability distribution to be any member of an exponential family of distributions. In this study a log-linear link function is preferred to a traditional linear model because of the nature of hospital discharge data. While predictors in a traditional linear model can take on any value, a log-linear function does not allow the predicted hospital discharge values to take on negative values. Furthermore, in this analysis, as hospital discharge data are of discrete nature, a Poisson distribution is assumed.

This implies that the number of observed monthly discharge data is assumed to be Poisson distributed random variable with mean and variance equal to a parameter λ specified as

$$\lambda_i = N_i \exp \sum_{j=1}^{12} \alpha_j M_j + \sum_{k=2}^{10} \beta_k J_k + \gamma F_i$$

or equivalently

$$\log \lambda_i = \log N_i + \sum_{j=1}^{12} \alpha_j M_j + \sum_{k=2}^{10} \beta_k J_k + \gamma F_i \ ,$$

where $i = 1, \ldots 120$ (monthly figures); N_i = size of the considered population in month i; $M_j = 1$ for calendar month j, $= 0$ elsewhere. $j = 1, \ldots 12$ (July–June); $J_k = 1$ for the kth year considered, $= 0$ elsewhere; $k = 1, \ldots 10$; F_i = influenza-activity indicator in month i.

The coefficients α_j, β_k, and γ have to be estimated. The coefficient γ represents the effects of influenza activity on hospitalization for a certain disease. The quantity $1 - \exp(-\gamma F_i)$ represents the excess hospitalization in month i as a proportion of λ_i. The presence of excess hospitalization is tested for by applying a two-tailed Student's t-test at a 5% significance level. The null-hypothesis is defined as $H_0: (1 - \exp(-\gamma F_i))$ $\lambda_i = 0$.

The decrease in deviance indicates the capacity of the model to explain the variation of the monthly hospital discharge rates. The figure R^2, which indicates the 'goodness of fit' of the model is estimated as:

$$R^2 = 1 - \exp[\{\text{deviance (fitted model)} - \text{deviance (unfitted model)}\}/\text{n}] \quad (27).$$

It is assumed that the monthly observed hospital discharges are mutually independent, given the explanatory variables year, month and influenza activity. To control for over-dispersion, the scale

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parameter was defined as the deviance divided by the number of degrees of freedom.

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