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## The public health impact of vaccination programmes in the Netherlands

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## Chapter 4

### **Years of life lost due to influenza-attributable mortality in older adults in the Netherlands: a competing risks approach**

The contents of this chapter have been published in the American Journal of Epidemiology:

**Years of life lost due to influenza-attributable mortality in older adults in the Netherlands:  
a competing risks approach**

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## **Abstract**

We estimated the influenza mortality burden in adults 60 years of age and older in the Netherlands in terms of years of life lost, taking into account competing mortality risks. Weekly laboratory surveillance data for influenza and other respiratory pathogens and weekly extreme temperature served as covariates in Poisson regression models fitted to weekly age-group specific mortality data for the period 1999/2000 through 2012/2013. Burden for age-groups 60–64 through 85–89 years was computed as years of life lost before age 90 (YLL90) using restricted mean lifetimes survival analysis and accounting for competing risks. Influenza-attributable mortality burden was greatest for persons aged 80–84 years, at 914 YLL90 per 100 000 persons [95% uncertainty interval (UI): 867, 963], followed by 85–89 years (787 YLL90 per 100 000; 95% UI: 741, 834). Ignoring competing mortality risks in the computation of influenza-attributable YLL90 would lead to substantial over-estimation of burden, from 3.5% for 60–64 years to 82% for persons aged 80–89 years at death. Failure to account for competing mortality risks has implications for accuracy of disease burden estimates, especially among persons aged 80 years and older. As the mortality burden borne by the elderly is notably high, prevention initiatives may benefit from being redesigned to more effectively prevent infection in the oldest age-groups.

## Introduction

Worldwide, infection with the influenza virus is responsible for considerable illness, hospitalisation, and mortality, especially among older adults and elderly persons (Simonsen et al., 2005, 2007), whose immune response is diminished compared with younger adults (Bernstein et al., 1999; Parodi et al., 2011). The mortality burden attributed to influenza virus infection is difficult to quantify from vital statistics data, because (i) death certificates often do not list influenza as an underlying or contributing cause when death is due to subsequent bacterial infection; (ii) influenza infection may serve to worsen existing chronic respiratory or circulatory disease so the chronic condition is entered as the underlying cause on the death certificate (Glezen et al., 2000); and (iii) laboratory confirmation of influenza infection is seldom done prior to death.

Given the public health significance of the large number of deaths presumed to be caused by influenza (e.g., influenza was estimated to have caused 11% of all deaths occurring in persons aged 65 years or older during the 2000–2009 influenza seasons in France (Bonmarin et al., 2015)) but are not registered as such (Sprenger et al., 1993), statistical modelling methods have been used to infer the true number of influenza-associated deaths from all-cause or cause-specific mortality data. Numerous studies have adopted an ecological approach to the estimation problem, by fitting generalised linear models that specify time series of positive tests for influenza and other co-circulating respiratory pathogens from virological surveillance systems as covariates, possibly adjusting for systematic seasonal variation and other factors, to estimate the time series of influenza-attributable mortality (Pitman et al., 2007; Goldstein et al., 2012; Van Asten et al., 2012; Charu et al., 2013; Green et al., 2013; Hardelid et al., 2013; Kessaram et al., 2015; Matias et al., 2016; Schanzer et al., 2013). Such methods exploit the seasonal patterns in pathogen activity, and are successful in that—given the modelling assumptions—the under-estimation in influenza mortality burden, if relying only on cause-of-death coding, can be overcome.

Although mortality is an important epidemiological indicator of the impact of an infectious disease in a population, the years of life lost (YLL) measure provides a more precise quantitative measurement of the burden of influenza (and other diseases) among the elderly than mortality incidence; with YLL, age at death (and

so the expected remaining healthy life-years) is incorporated. The more prematurely that death occurs, the higher the burden. Particularly for the elderly population, for whom the prevalence of chronic multi-morbidity is high (Marengoni et al., 2008; Van den Akker et al., 1998), it is vital to compute YLL for influenza treating death from other causes as competing risks. The implicit assumption when calculating YLL associated with a single cause of death such as influenza is that removing this cause of death from the population would have no effect on the probability of dying from other causes. However, this independence assumption is in general not viable (Allignol et al., 2011; Andersen et al., 2012). To avoid over-estimation of population-level total mortality burden, the YLL associated with each possible cause of death should sum exactly to the YLL calculated on the basis of all-cause mortality, and appropriate estimation methods are therefore required to ensure that cause-specific YLL correctly acknowledges competing mortality risks (Lai and Hardy, 1999; Andersen, 2013; Van Wijhe et al., 2016). The relevance of this issue grows with the probability of death from other causes; i.e., with increasing age.

Thus, the principal objective of the current study is to estimate the weekly and annual mortality burden from influenza in adults 60 years of age and older in terms of YLL, taking into account competing mortality risks. Our secondary objective was to compare this measure to 'standard' YLL, which ignores competing mortality risks.

## Methods

### *Study design and period*

To model influenza-attributable deaths we considered mortality from any cause as the primary dependent variable. We also considered two other, more specific, cause-of-death categories: circulatory/respiratory causes and respiratory-only causes (Charu et al., 2013; Van den Wijngaard et al., 2010). The latter was defined as cause of death codes J00–J99 (ICD-10) or 460–519 (ICD-9), and the former was supplemented with the circulatory disease codes I00–I99 (ICD-10) and 390–459 (ICD-9).

The study period was defined as the 1999/2000 through 2012/2013 influenza seasons. Because death certificate coding practice changed from the beginning of 2013, leading to notable changes in distribution over certain cause-of-death code categories, for the two more specific mortality outcomes the study period was defined to end one season earlier, at 2011/2012.

### *Data sources*

All deaths in the Netherlands are registered with Statistics Netherlands. Weekly mortality data with primary cause of death information, stratified by 5-year age-group (60–64 through 80–84 years, and additionally 85+ years), were obtained for the period 1999–2013. Causes of death were coded using ICD-10. Because influenza circulates mainly during the winter months, seasons were defined as week 40 of a given year through week 39 of the following year.

Routine weekly surveillance data on positive laboratory results for a range of respiratory pathogens have been reported since 1989. Between 17 and 21 laboratories in the Netherlands submit weekly reports to a centralised database (the Weekly Surveillance System of the Dutch Working Group on Clinical Virology (Dutch Working Group on Clinical Virology, 2016)). From these data, we counted PCR-confirmed positive samples for the following viral and bacterial agents: influenza A/B, respiratory syncytial virus, rhinovirus, parainfluenza, and *Mycoplasma pneumoniae*. We extracted data from 1999/2000 through 2012/2013, with seasons defined similarly as for mortality.

### *Poisson regression modelling of influenza-attributable mortality*

In common with the general ecological modelling approach used in previous research (Pitman et al., 2007; Goldstein et al., 2012; Van Asten et al., 2012; Charu et al., 2013; Green et al., 2013; Hardelid et al., 2013; Schanzer et al., 2013; Kessaram et al., 2015; Matias et al., 2016), we assumed that seasonal variability in mortality can be explained, in part, by temporal variation in the reporting incidence of various respiratory pathogens. The proportion of mortality attributable to influenza can then be determined after adjusting for the co-circulation of other pathogens and other factors via linear regression techniques. We assumed additivity in this relationship for simplicity (i.e., a given death cannot be caused by more than one respiratory pathogen).

Separate Poisson regression models, with identity link function to enable an additive interpretation of model coefficients, were fitted to the weekly mortality data for each age-group. Laboratory virological surveillance data were not available stratified by age; therefore each age-group specific regression model adjusted for the total positive samples reported for the pathogen.

*Covariates.* Besides influenza A (coded using separate variables for each season, to capture seasonal variation in severity), the candidate pathogen covariates considered were influenza B, respiratory syncytial virus, rhinovirus, *Mycoplasma pneumoniae*, and parainfluenza. Temperature is known to be an important correlate of mortality (Kunst et al., 1993; Donaldson and Keatinge, 2002), although the relationship is not straightforward, as it may be that only periods of extreme cold and heat influence the risk of death. We defined two covariates for temperature extremes, by first calculating the average weekly temperatures ( $T$ , in degrees Celsius) from daily temperatures recorded at the de Bilt (centrally located in the Netherlands) weather station and made available online by the Royal Netherlands Meteorological Institute (Royal Netherlands Meteorological Institute (KNMI), 2016), and then coding low extreme temperature using the function  $\max(0, 5 - T)$  and high extreme as  $\max(0, T - 17)$  (Van Asten et al., 2012). This coding effectively treats temperatures as extreme if below 5C or above 17C.

*Model selection.* A defined model selection procedure was carried out for each age-group separately. First, linear and quadratic terms were entered to model temporal trends in mortality (and so avoid over-estimation of attribution to influenza or the other pathogens). We term this the *base* model. We next considered the impact of 0- to 4-week lags between weekly surveillance reports of influenza A and B and other co-circulating pathogens and mortality (Van Asten et al., 2012). Respiratory pathogens were explored one at a time using a forward selection procedure: each lagged covariate was added independently to the base model, with the lag associated with the largest AIC reduction selected. Next, to the base model now augmented with the selected lags for influenza A and B and the other respiratory pathogens, low and high extreme temperature terms were specified, and trigonometric terms were added to account for the assumed sinusoidal-shaped background mortality (modelling seasonal variation due to other causes). Next, pathogen covariates with negative coefficients were removed on grounds of biological implausibility (it is not plausible that pathogen infection would decrease the risk of death). Finally, the single influenza A term was replaced with 14 separate season-specific influenza coefficients; if any of these coefficients were negative, the model was refitted after removing these terms. Models were therefore fitted of the form:

$$E(Y_i) = \beta_0 + \gamma_1 w_i + \gamma_2 w_i^2 + \sum_{s=1}^N (\alpha_s Z_{s,i}) + \sum_{j=1}^n (\beta_j X_{(i-t_j)j}) + \gamma_3 T_{\text{high},i} + \gamma_4 T_{\text{low},i} + \gamma_5 \sin\left(\frac{2\pi i}{52.143}\right) + \gamma_6 \cos\left(\frac{2\pi i}{52.143}\right) \quad (4.1)$$

We use the index  $i$  to refer to the week of the study period, the index  $j$  to refer to the pathogen, and the index  $s$  to refer to the season.  $Y$  is assumed to follow a Poisson distribution.  $Y_i$  is the observed number of deaths in week  $i$ ,  $\beta_0$  is a constant (or intercept) term; the next terms capture linear and quadratic temporal trends with  $w_i$  defined as the  $i$ th week in the study period.  $N$  is the total number of seasons for which season-specific influenza A coefficient  $\alpha_s$  is non-negative,  $Z_{s,i}$  are the weekly laboratory reported positive influenza A samples within season  $s$ ,  $X_{i,1\dots n}$  are the weekly laboratory reported positive samples for up to  $n$  co-circulating pathogens (i.e., model fit-based selection from: influenza B, respiratory syncytial virus, rhinovirus, parainfluenza, and *Mycoplasma pneumoniae*), with potential lag of  $t_j$  weeks. Additional included terms are for extreme temperature:  $T_{\text{high},i}$  and  $T_{\text{low},i}$ , and the two harmonic terms:  $\sin\left(\frac{2\pi i}{52.143}\right)$  and  $\cos\left(\frac{2\pi i}{52.143}\right)$ . The same procedure was applied to fit regression models to circulatory/respiratory and respiratory-only underlying cause mortality data. We constructed 95% prediction intervals (PIs) around predicted weekly influenza-attributable deaths using bootstrapping methods.

### *Computation of years of life lost (YLL)*

YLL are standardly defined as the number of cause-specific deaths multiplied by the expected number of healthy life-years lost conditional on the age at death. This residual life expectancy (LE) is defined as how long a person would expect to live in an ideal world that is free of disease assuming access to health care. For instance, the WHO Global Health Estimates projected LE values for 2050, citing a LE at birth of 92 years (World Health Organization, 2013).

Andersen (2013) definition of YLL computed in a competing risk framework requires estimation of cause-specific cumulative risks of death, which in turn requires age- and/or time-specific cause-specific mortality data. Note that this approach differs



from the 'standard' YLL definition, in that the  $\tau$ -restricted mean lifetime method from survival analysis is used instead of adopting age-specific LE from life tables. We defined  $\tau = 90$ , so we effectively calculate YLL based on a LE of 90 years. We denote this variant of YLL as 'YLL90', which can be interpreted as the expected number of life years lost before reaching the age of 90. To quantify the anticipated over-estimation of mortality burden that would occur if competing mortality risks were ignored, we compare YLL90 to YLL computed based on Kaplan-Meier survival curves (see Supplementary information to Chapter 4).

The estimation of YLL90 was carried out using a simulation procedure applied to conditional survival functions defined for 'cohorts' consisting of all persons within each age-group at death (see Supplementary information to Chapter 4 for a detailed description). Cumulative mortality incidence curves were then constructed for (i) influenza-attributable deaths, and (ii) all other causes of death, and YLL90 for each cause category calculated accordingly (Supplementary information to Chapters 2 and 4; see also Andersen (2013); Van Wijhe et al. (2016)). This simulation procedure was repeated 1000 times, with the uncertainty inherent in the resulting age-group specific distributions of influenza-attributable YLL90 combined with the 95% PIs for predicted influenza-attributable deaths, yielding 95% uncertainty intervals (UIs) for YLL90.

Within each iteration, YLL90 was calculated for each age-group and season, simulating conditional survival functions based on the weekly predicted number of influenza-attributable deaths derived from the corresponding fitted Poisson models and the national population estimates (see Supplementary information to Chapter 4 for further details).

### *Outcomes and statistical analysis*

We present the weekly and annual YLL90 due to influenza-attributable mortality both in absolute terms, and also as the proportion of annual total YLL90 within the entire outcome category (all-cause, circulatory/respiratory, or respiratory only); thus considering deaths from causes other than influenza as competing risks. The latter measure—proportion of total YLL90—permits declining secular trends in mortality to be taken into account. In addition, to allow comparisons of mortality burden between age-groups, we report YLL90 per 100 000. This measure controls for

differences in age-group population size (and thus adjusts for demographic change; i.e., the growing and ageing Dutch population (National Kompas Volksgezondheid (NKV), 2016)) so that influenza mortality burden can be meaningfully compared across age-groups. Finally, inter-season variability was quantified as the standard deviation of the YLL90 per 100 000 measure. All modelling was conducted in the R statistical programming environment, version 3.2.0 (R Development Core Team, 2015).

## Results

The total number of influenza-attributable deaths in persons aged 60+ years ranged from 40 to 3330 over season (1.3% of all deaths) and varied by age-group, with the highest influenza mortality rate estimated for the 85+ years age-group (see Supplementary Table 4.3 and Supplementary Figure 4.3). Models fitted to more specific cause-of-death data (i.e., respiratory/circulatory underlying causes, and respiratory causes only) showed similar temporal patterns, but with smaller absolute numbers (Supplementary Figures 4.4 and 4.5).

### *Years of life lost before age 90*

Influenza-attributable mortality burden exhibited considerable seasonal variability, with YLL90 ranging from 480 to 30 680 across seasons within the study period (Table 4.1). The 85–89 years age-group, although contributing the largest estimated number of influenza-associated deaths (1.7% of the cumulative total registered deaths in this age-group over the study period), did not incur the largest absolute influenza-attributable burden; this was observed for the 80–84 years group, with across-season average YLL90 of 2992 (Table 4.2).

Between 0.04% and 2.37% of the total YLL90 per season in persons aged 60–89 years was attributed to influenza (Table 4.1 and Figure 4.1). This proportion measure, which adjusts for any secular changes in overall mortality risk, tended to decrease over the study period. The 85–89 years age-group was responsible for the largest age-group specific share of the total mortality burden (1.61%) (Table 4.2).

Estimates using more specific cause-of-death data—respiratory/circulatory underlying causes and respiratory causes only—were comparable to the all-cause results,

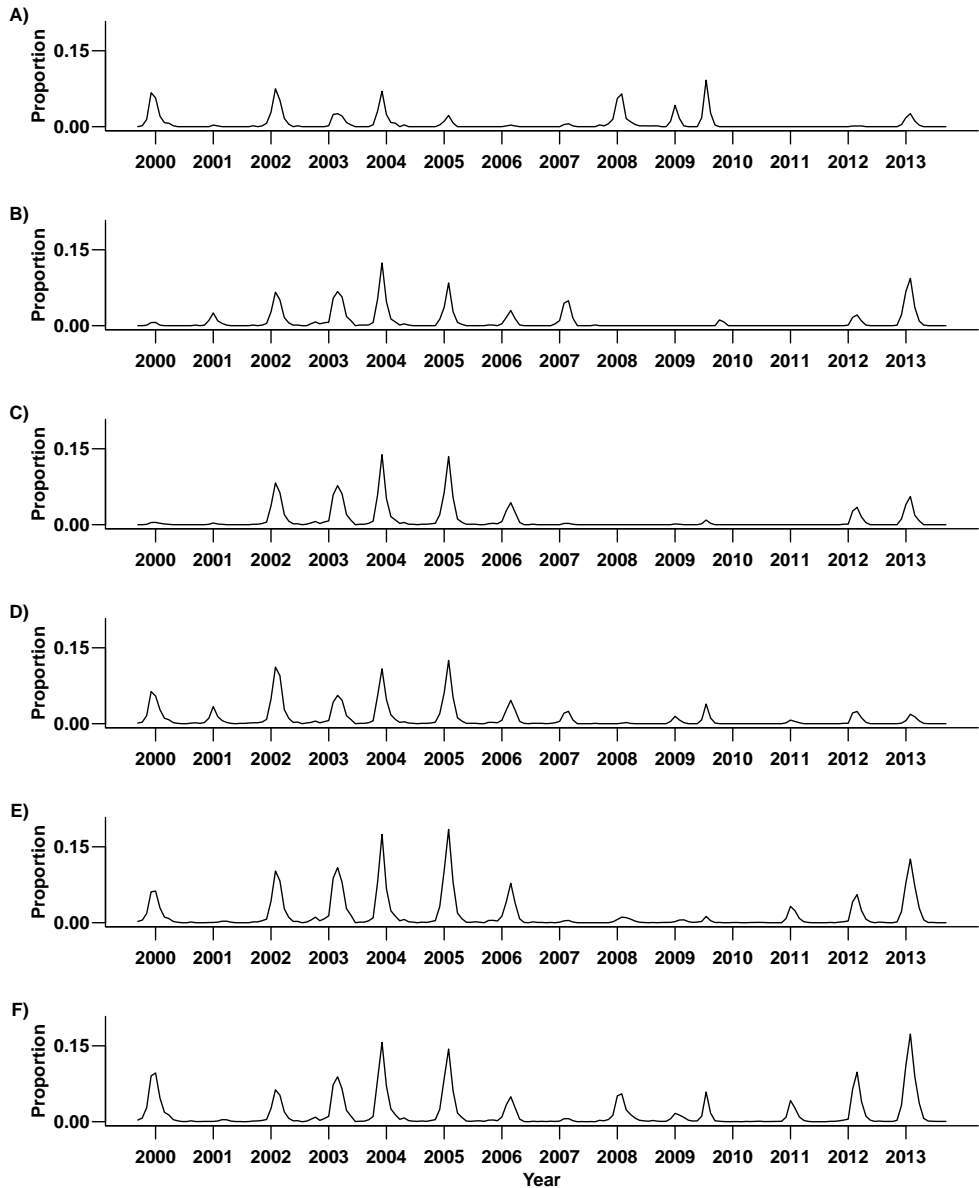
**Table 4.1: Total and influenza-attributable YLL90 for persons aged 60–89 years, the Netherlands, seasons 1999/2001 through 2012/2013.** Shown are the total and the proportion of total YLL90 attributable to influenza, and influenza-attributable YLL90 per 100 000 stratified by 5-year age-group at death. Temporal variability in YLL90 per 100 000 per age-group is indicated by the standard deviation (SD). Data is based on all-cause mortality. Only point estimates are shown.

Season	YLL90			Influenza-attributable YLL90 per 100 000					
	Total	Influenza-attributable	Proportion (%)	60–64	65–69	70–74	75–79	80–84	85–89
1999/2000	1 343 300	14 580	1.09%	430	50	60	997	1176	1333
2000/2001	1 334 700	3340	0.24%	18	170	25	374	45	57
2001/2002	1 347 400	25 860	1.92%	437	540	914	1617	1598	746
2002/2003	1 331 800	24 120	1.81%	168	681	995	862	1894	1235
2003/2004	1 295 400	30 680	2.37%	330	782	1172	1248	2057	1610
2004/2005	1 306 100	28 370	2.17%	99	486	1143	1363	2349	1464
2005/2006	1 263 900	10 500	0.83%	12	166	395	517	945	539
2006/2007	1 230 100	4180	0.34%	24	320	24	252	55	63
2007/2008	1 258 000	5890	0.47%	345	4	0	13	171	647
2008/2009	1 258 800	8020	0.64%	427	10	8	362	91	469
2009/2010	1 289 900	480	0.04%	3	42	0	0	13	19
2010/2011	1 261 100	2370	0.19%	3	0	2	58	314	291
2011/2012	1 297 900	8530	0.66%	10	108	245	229	580	812
2012/2013	1 320 800	21 170	1.60%	120	543	401	158	1503	1730
Inter-season variability (SD)				175	281	464	543	831	578

YLL: Years of life lost.

in showing similar decreasing temporal trends in the proportion of total YLL90 attributed to influenza (Supplementary Figures 4.6 and 4.7), and similar rankings of this proportion over age-group. However, lower absolute YLL90 and YLL90 per 100 000 rates (Supplementary Tables 4.4 and 4.5) were obtained, due to smaller numbers of influenza-attributed deaths.

Influenza-attributable YLL90 per 100 000 persons for all-cause mortality is depicted in Supplementary Figure 4.8. The YLL90 rates for the younger age-groups (i.e., 60–64, 65–69 years) varied widely across seasons of the study period, but variation in the burden was even more pronounced for persons aged 80–89 years (Figure 4.2 and Table 4.1). A similar age pattern was observed if YLL90 is calculated using more specific cause-of-death data (Supplementary Figures 4.9 and 4.10). When standardising for age-group population size and aggregating over season, the highest burden (YLL90 of 914 per 100 000; 95% UI: 867, 963) was observed for the 80–84 years age-group, with the second highest burden (787 per 100 000; 95% UI:



**Figure 4.1: Contribution of influenza to total YLL90 by age-group, the Netherlands, seasons 1999/2000 through 2012/2013.** Proportion of total YLL90 attributable to influenza based on all-cause mortality data, aggregated to 4-week intervals for the period 1999/2000 through 2012/2013. Each age-group is shown as a separate panel: (A) 60–64 years; (B) 65–69 years; (C) 70–74 years; (D) 75–79 years; (E) 80–84 years; and (F) 85–89 years.

**Table 4.2: Comparison of age-group specific influenza-attributable YLL90 in the Netherlands, seasons 1999/2000 through 2012/2013.** Shown are averages over seasons 1999/2000 through 2012/2013. Data is based on all-cause mortality.

Age-group (years)	Influenza-attributable YLL90			Influenza-attributable YLL (Kaplan-Meier survival) <sup>2</sup>		
	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])
60–64	1493	0.67%	173 [152, 199]	1544	0.69%	179 [157, 205]
65–69	1980	0.82%	279 [255, 303]	2116	0.87%	297 [272, 323]
70–74	2243	0.84%	385 [357, 415]	2492	0.93%	427 [396, 460]
75–79	2658	1.00%	575 [540, 613]	3106	1.17%	671 [629, 716]
80–84	2992	1.50%	914 [867, 963]	4095	2.03%	1236 [1173, 1303]
85–89	2053	1.61%	787 [741, 834]	5055	3.70%	1878 [1782, 1981]
All [60–89] <sup>1</sup>	13 433	1.03%	423 [412, 435]	18 468	1.40%	573 [559, 589]

YLL: Years of life lost; UI: uncertainty interval.

<sup>1</sup> Influenza-attributable YLL90 or YLL for individual age-groups do not sum to the value for *All [60–89]*, as the latter was computed using the aggregated age-group 60–89 years.

<sup>2</sup> YLL based on Kaplan-Meier Survival, and so does not account for competing mortality risks.

741, 834) for persons aged 85–89 years (Table 4.2). YLL90 for these two age-groups is notably high, as YLL90 for the age-group with next highest burden, 75–79 years, was 37% lower, at 575 per 100 000 [95% UI: 540, 613]. Ignoring competing mortality risks tended to over-estimate the overall mortality burden. For persons aged 60–64 years at death, YLL computed based on Kaplan-Meier survival curves yielded an overall 3.5% higher total mortality burden attributed to influenza compared with YLL90 (Table 4.2). However, the extent of over-estimation increased with age; for persons aged 80–89 years, over-estimation was 82%.

## Discussion

In terms of the estimated number of influenza-attributable deaths the highest burden was observed for persons aged 85 years and older. However, the YLL90 measure provides an alternative view of mortality burden by taking into account age at death and competing risks of death from other causes. Of the total YLL90 calculated from all-cause mortality, the greatest proportion attributable to influenza—1.61%—was also among persons aged 85–89 years. The next youngest age-groups (80–84 years and 75–79 years) had the second and third largest influenza-attributable shares of the mortality burden. However, the age-standardised mortality burden measure

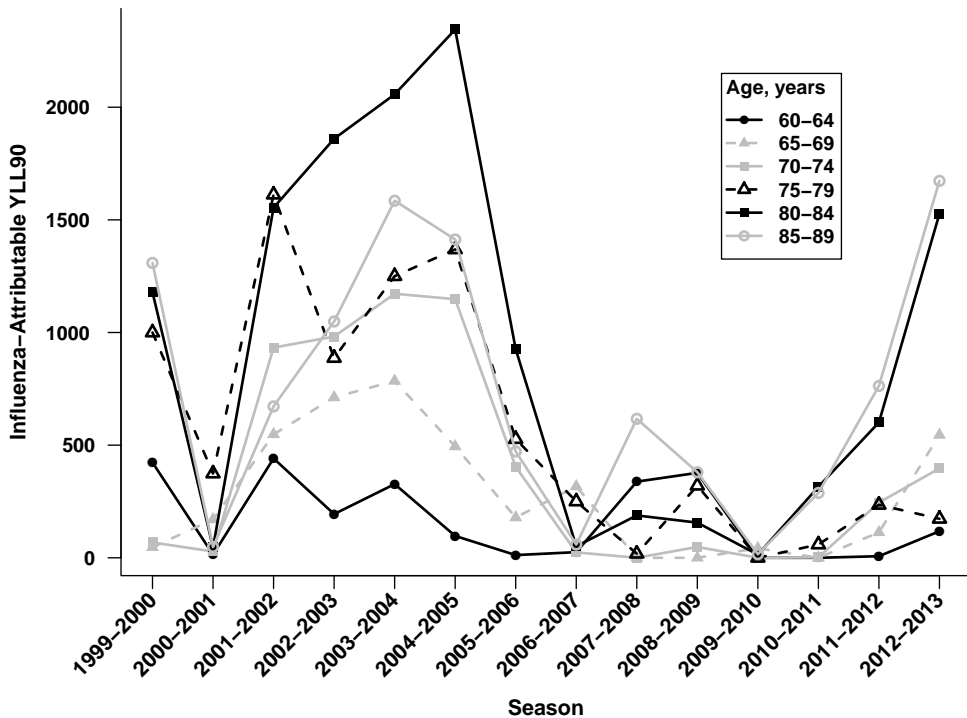


Figure 4.2: Median influenza-attributable YLL90 per 100 000 by season and age-group, the Netherlands, seasons 1999/2000 through 2012/2013. Data is based on all-cause mortality, aggregated by season, and plotted separately by 5-year age-group.

YLL90 per 100 000 localised the highest mortality burden to the 80–84 years age-group, followed by the 85–89 years age-group.

Our estimates of the proportion of total YLL90 per season in 60- to 89-year-olds that is due to influenza, although small on average (ranging from 0.04% to 2.37% across seasons; Table 4.1), are also lower than if YLL is computed ignoring competing mortality risks. Age-group specific burden varied between the two measures; for persons aged 80–89 years, the latter YLL measure yielded a notably higher (82%) estimated mortality burden. This suggests that competing risks for mortality in the elderly should be considered when estimating influenza mortality burden using statistical modelling approaches.

The age group-specific influenza-attributable proportion ranged from an across-season average of 0.67% for 60- to 64-year-olds to an average of 1.61% for 85- to 89-year-olds (Table 4.2). However, averaging influenza-attributable mortality burden obscures variation over time. There was also substantial variation in age-group specific YLL90 per 100 000, particularly for persons 80 years and older (Figure 4.2), which suggests that variation in season severity may disproportionately affect the most aged segment of the population (Lofgren et al., 2007). This variation reflects a complex interplay between the circulating virus strain distribution, vaccine mismatch, and degree of natural immunity (Viboud and Epstein, 2016).

The temporal patterns and magnitude of influenza-attributable mortality we obtained were comparable to previous statistical modelling exercises conducted using Netherlands data for wider age-groups. Van Asten et al. (2012) estimated that 1.5% of total deaths in 65-year-olds and over in the period 1999–2007 was due to influenza A; we observed 1.4% of total deaths due to influenza A/B for the same age group in the longer period 1999 through 2013. Van den Wijngaard et al. (2010) calculated annual age-specific YLL for the period 1999 through 2010 (however, not taking competing mortality risks into account and using lower LE norms), and reported total YLL per season that varied from 0 to approximately 18 000 for person aged 75+ years. Our estimated YLL90 range for the same age-group over our study period was 102 to 17 630, which is necessarily lower due to the incorporation of competing mortality risks in the YLL90 calculation.

Consistent with previous research (Van den Wijngaard et al., 2010; Wielders et al., 2012), we observed a relatively low influenza mortality burden among older adults—0.04% of total YLL90 based on all-cause deaths—for the 2009/2010 pandemic year. Other than for 2009/2010, for which 100% of influenza A samples were subtype H1N1 and for 2003/2004, for which 100% were H3N2 (Darvishian et al., 2017), there was no clear correspondence between seasonal total YLL90 and dominant circulating virus type.

We used all-cause mortality in the main analysis. Because influenza infection plays a larger role for certain causes of death, one can also estimate burden based on more specific cause-of-death categories. Supplementary analyses using circulatory/respiratory and respiratory-only mortality data were largely consistent

with the results based on all-cause mortality. Although the estimated influenza-attributable YLL90 and YLL90 per 100 000 were lower, the greater mortality burden for persons 80–89 years was replicated.

Attribution of influenza-caused mortality via Poisson regression is technically challenging and is consequently subject to several limitations (Simonsen and Viboud, 2012). First, through inclusion of harmonic terms to capture seasonal patterns in mortality unaccounted for by the included covariates, we effectively made the assumption that the impact of these unmeasured influences is static across seasons. This could lead to over- or under-estimation of the associations between the activity of other pathogens and mortality in a given season; alternative regression modelling techniques may improve model fit (Muscatello et al., 2014). Related to this issue, by fitting a single, time-invariant regression coefficient for each circulating pathogen other than influenza A, the number of weekly deaths attributable to these pathogens was constrained to be a constant proportion of the reported positive tests. Finally, we assumed that there were no historical changes in testing/reporting that would affect the laboratory surveillance data.

As age at death was available only at a granularity of five years, our method randomly allocated an age at death for the calculation of cumulative mortality incidence and YLL90. This led to lower precision in age-specific YLL90 than if the exact age at death were known. The restricted mean lifetime approach requires definition of a maximum attainable age. Using a higher limit, e.g., 95 years, would inflate the estimated absolute YLL90 and YLL90 per 100 000 values, but age group-specific proportions would not change appreciably.

Our quantitative estimation of the mortality burden due to influenza in the Netherlands over a 14-season analysis period indicates that the greatest burden, adjusting for population size, is borne by persons aged 80 years and over, and is highest for the 80–84 age-group. The more aged segment of persons targeted by the Dutch national influenza prevention programme has a historically higher vaccination uptake (75+ years: 85% in 2008) than younger eligible persons (65–74 years: 73% in 2008) (Statistics Netherlands (CBS), 2011), but uptake does not translate directly into protection. Although the single large randomized trial conducted to date yielded a vaccine efficacy (VE) of 59% [95% CI: 20%, 79%] for the youngest (60–69 years) decade of our study population (Govaert et al., 1994), evidence regarding VE of the (inactivated)



flu vaccine for persons aged 70 years and over is lacking. As the Dutch residual life expectancy upon reaching one's 80<sup>th</sup> birthday is about nine years, substantial mortality burden could be averted by preventing influenza in the elderly. Given the large observed degree of inter-season variability in mortality burden borne by the oldest age-groups—related to the strain distribution, vaccine mismatch (De Jong et al., 2000), virus pathogenicity, vaccination coverage, and drivers of transmission—the most vulnerable elderly may benefit from being targeted for further prevention measures as supplement to routine flu vaccination.

### **Declaration of interests**

The authors have no conflicts of interest to declare.

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## Supplementary information to Chapter 4

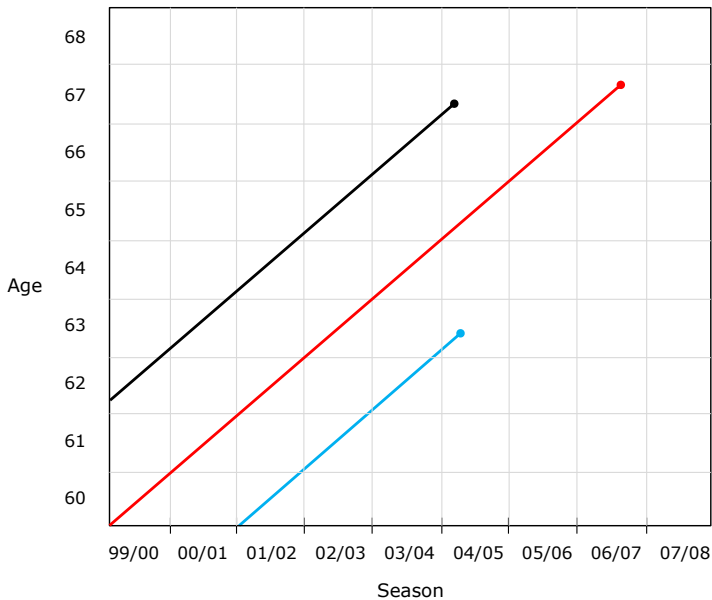


## Simulation of cumulative mortality curves conditional on being alive at age $y$

Conditional survival functions (ie., conditional on being alive at age  $y$ ) were defined for 'cohorts' constructed from all members of all age-groups at death. Entry to follow-up for each cohort was defined as turning age 60 (i.e.,  $y$  was set to 60 years). Given the coarse age-granularity of the mortality data, age of death was simulated within each five-year age interval by randomly sampling discrete ages at death from a uniform distribution. For the oldest age-group we assumed a uniform distribution between 85 and 89 years. The simplification of treating deaths occurring after  $\tau = 90$  years as occurring within the interval 85 to  $<90$  has little impact, as relatively few deaths were recorded in persons  $\geq 90$  years: 16% of all deaths in those aged 60+ years in the period 1999/2000 to 2012/2013 occurred at  $\geq 90$  years ((Statistics Netherlands (CBS), 2016)).

After age of death was assigned, the season-cohort to which each individual belonged (i.e., the season in which he/she turned 60 years old) could be determined. For instance, persons dying at age 68 years entered follow-up on first day of the season in which their 60<sup>th</sup> birthday fell (see Supplementary Figure 4.1 for simplified example life trajectories plotted as a Lexis diagram), but follow-up was constrained to begin no earlier than the beginning of the 1999/2000 season. Thus, for deaths in the older age-groups in the earlier seasons, follow-up necessarily started at their age in 1999/2000 (e.g., black trajectory, Supplementary Figure 4.1). Deaths were actually simulated to fall within either the upper or lower 'Lexis triangle' within a given square of the season-by-age grid; this depended on the week of the season in which the death was recorded. Thus, individuals who died at age  $a$  in season  $s$  and who had a simulated life trajectory with end point in the lower Lexis triangle were assigned to age cohort  $(a - 60)$  in season 0, where  $s = 0$  for 1999/2000,  $s = 1$  for 2000/2001, etc. Those whose simulated trajectory ended in the upper Lexis triangle were assigned to age cohort  $(a - 60 + 1)$  in season 0. For individuals with start of follow-up after season 0, assignment was to age cohort 60 in season  $(s - (a - 60))$  (upper Lexis triangle) or to age cohort 60 in season  $(s - (a - 60 - 1))$  (lower Lexis triangle). Next, total cohort membership at entry to follow-up for each age cohort in 1999/2000 (and for each of the 13 cohorts of individuals turning 60 in seasons 2000/2001 through 2012/2013) was assigned based on the national age-specific population size for the season. The latter was determined as the population on 1st

January falling within the season ((Statistics Netherlands (CBS), 2016)). There is now sufficient information to construct conditional survival curves for each age/season cohort.



**Supplementary Figure 4.1: Example of a Lexis diagram (2).** Lexis diagram with example trajectories for three individuals. The black and red individuals both died at age 67; for the death in the 2006/2007 season, follow-up started at age 60, at the beginning of season 1999/2000; for the person who died in 2004/2005, follow-up began at age 62 in 1999/2000. The blue individual, who died at age 63 in season 2004/2005 could only be followed-up starting in 2000/2001, from age 60.

## Computation of cause-specific YLL90

After constructing cause-specific cumulative mortality incidence curves (using the Aalen-Johansen estimator) for each age/season cohort, for influenza and other causes of death, YLL90 for each cumulative incidence curve corresponding to the interval of interest, e.g. the incidence in a particular season multiplied by the period between age at death and age 90 and the starting population size of the cohort (see Andersen (2013) and Supplementary information to Chapter 2).

Specifically, if  $\tau_0$  is the age at entry to follow-up and  $\tau$  is the maximum possible lifespan in years, the expected years of life lost between age  $\tau_0$  and age  $\tau$  due to cause  $j$ ,  $L_j$ , is:

$$L_j(\tau_0, \tau) = \int_{\tau_0}^{\tau} \hat{F}_j(t) dt \quad (4.2)$$

where  $\hat{F}_j(t)$  is the Aalen-Johansen estimator for the cause  $j$  cumulative mortality incidence, and is the closed-form expression (where  $\hat{S}$  is the Kaplan-Meier estimator,  $d_{j,i}$  is the number of deaths from cause  $j$  at time  $t_i$ ;  $n_i$  is the number of persons at risk at time  $t_i$ ):

$$\hat{F}_j(t) = \sum_{i:t_i \leq t} \hat{S}(t_{i-1}) \frac{d_{j,i}}{n_i} \quad (4.3)$$

The sum over each cause-specific YLL,  $L_j$ , and the Kaplan-Meier estimator,  $\hat{S}$ , for survival between  $\tau_0$  and  $\tau$  necessarily satisfies the balance equation:

$$\int_{\tau_0}^{\tau} \hat{S}(t) dt + \sum_{j=1}^k L_j \tau_0, \tau = \tau - \tau_0 \quad (4.4)$$

The above equation states that the number of years of life lost between age  $\tau_0$  and age  $\tau$  due to all causes  $j$ , plus the years of life lived, should equal the difference between the starting cohort age and the maximum lifespan. This balance equation is what differentiates the competing risk method for deriving cause-specific years of life lost from a method using Kaplan-Meier (K-M) survival curves to estimate cause-specific years of life lost. For each age/season cohort separately, we can therefore estimate the number of years of life lost due to each cause  $j$ , while taking into account the competing risk of mortality from other causes.

## Comparison of YLL90 with YLL derived from Kaplan-Meier survival

We next defined years of life lost for a given cause, but ignoring competing mortality risks; this we term Kaplan-Meier based years of life lost. This is comparable to the 'standard' definition of YLL for a given cause (ie. disease, injury or condition), which is calculated as remaining life expectancy at age of death. Summed 'standard' YLL calculated separately for a number of causes can be paradoxically greater than the total YLL 'possible' (when calculated for deaths from any cause).

In the Kaplan-Meier based YLL approach, the expected years of life lost (with respect to the maximum possible lifespan  $\tau$ ) for cause  $\tau$  are defined as:

$$L_j(\tau_0, \tau) = \int_{\tau_0}^{\tau} \hat{G}_j(t) dt \quad (4.5)$$

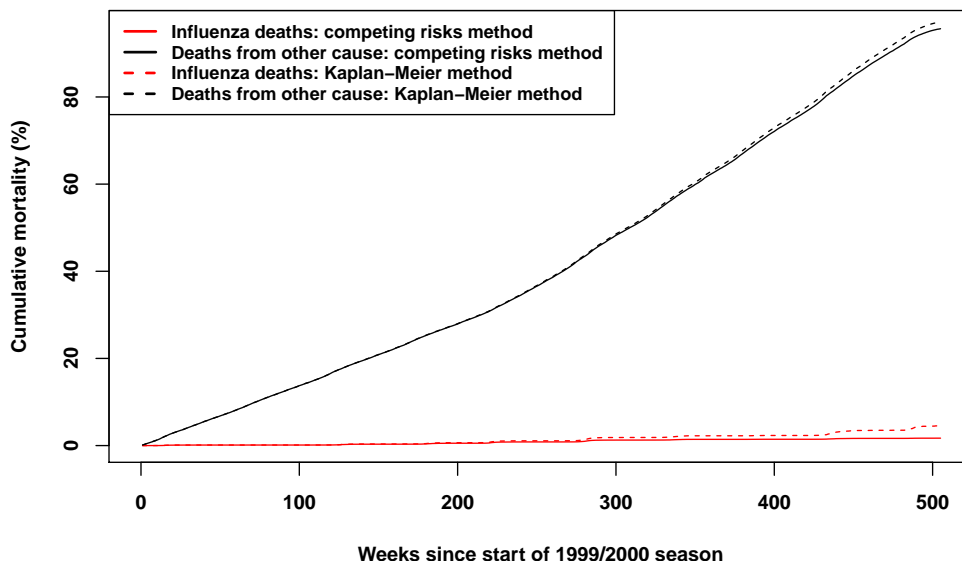
where the cumulative mortality incidence due to cause  $j$ ,  $\hat{G}_j$  is estimated as one minus the cumulative survival probability ('1 - K-M estimate'), defined as follows:

$$\hat{S}_j(t) = \prod_{t_i \leq t} \frac{n_{i-1} - d_{j,i}}{n_{i-1}} \quad (4.6)$$

$$\hat{G}_j(t) = 1 - \hat{S}_j(t) \quad (4.7)$$

where  $d_{j,i}$  is the number of deaths from cause  $j$  at time  $t_i$  and  $n_i$  is the number of persons at risk at time  $t_i$  (in which deaths from other causes are considered censoring events). Note that this definition of YLL will not satisfy the balance equation above.

To illustrate the difference between YLL90, and YLL based on Kaplan-Meier survival calculated separately for influenza and for other causes of death, we graphically compare cumulative incidence of mortality curves computed using the present competing risk approach, to cumulative mortality curves computed based on Kaplan-Meier survival (1 - K-M estimate). As an example, consider the cohort of 80-year-olds commencing follow-up at the beginning of season 1999/2000 (Supplementary



**Supplementary Figure 4.2: Example cumulative mortality incidence curves.** Influenza mortality computed using the Aalen-Johansen estimator is compared with the Kaplan-Meier method. Starting cohort is a cohort of 80-year-olds in season 1999/2000. Data is based on all-cause mortality data.

Figure 4.2). This cumulative mortality incidence plot indicates that the K-M method slightly over-estimates influenza-attributable mortality, and thus would over-estimate YLL due to influenza. The curve for cumulative mortality attributable to influenza is upwardly biased when competing mortality risks from other causes are ignored (because death from other causes is incorrectly treated as a censoring event, which assumes that persons would still be at risk of dying from influenza had they been followed-up longer), compared with when competing risks are taken into account.

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**Supplementary Table 4.3: Estimated age-specific influenza-attributable mortality rates, the Netherlands, seasons 1999/2000 through 2012/2013.** Mortality rate are in deaths per 10 000 persons. Values in square brackets are 95% prediction intervals.

Season	Age-group at death in years					
	60–64	65–69	70–74	75–79	80–84	≥85
1999/2000	1.6 [1.5, 1.8]	0.22 [0.20, 0.25]	0 [0, 0]	7.8 [7.4, 8.2]	14.0 [13.3, 14.7]	49.9 [47.3, 52.9]
2000/2001	0 [0, 0]	0.81 [0.73, 0.85]	0 [0, 0]	3.1 [3.0, 3.2]	0.55 [0.49, 0.62]	2.0 [1.9, 2.0]
2001/2002	1.6 [1.5, 1.7]	2.3 [2.2, 2.4]	4.9 [4.7, 5.1]	12.8 [12.3, 13.5]	20.6 [20.0, 21.4]	26.8 [26.1, 27.9]
2002/2003	0.53 [0.49, 0.58]	3.0 [2.9, 3.1]	5.7 [5.5, 6.0]	6.2 [6.1, 6.5]	24.3 [23.8, 24.9]	42.4 [41.4, 43.5]
2003/2004	1.1 [1.0, 1.2]	3.3 [3.2, 3.5]	6.6 [6.2, 6.9]	9.5 [9.0, 9.8]	25.9 [25.0, 27.3]	59.3 [56.5, 61.4]
2004/2005	0.25 [0.23, 0.28]	1.9 [1.8, 2.1]	6.4 [6.2, 6.7]	10.1 [9.7, 10.5]	30.3 [29.4, 31.4]	55.4 [50.9, 57.8]
2005/2006	0 [0, 0]	0.69 [0.66, 0.75]	2.2 [2.1, 2.3]	3.8 [3.7, 4.0]	12.1 [11.7, 12.7]	18.8 [18.1, 19.6]
2006/2007	0 [0, 0]	1.5 [1.4, 1.6]	0 [0, 0]	2.1 [2.0, 2.2]	0.59 [0.56, 0.65]	2.3 [2.3, 2.5]
2007/2008	1.3 [1.2, 1.4]	0 [0, 0]	0 [0, 0]	0.06 [0.04, 0.08]	1.5 [1.4, 1.6]	24.2 [23.3, 25.3]
2008/2009	1.6 [1.5, 1.8]	0 [0, 0]	0 [0, 0]	2.9 [2.7, 3.0]	0.88 [0.82, 0.93]	16.5 [15.7, 19.1]
2009/2010	0 [0, 0]	0.19 [0.17, 0.21]	0 [0, 0]	0 [0, 0]	0.17 [0.11, 0.20]	0.67 [0.64, 0.67]
2010/2011	0 [0, 0]	0 [0, 0]	0 [0, 0]	0.32 [0.30, 0.35]	3.9 [3.6, 4.0]	11.0 [10.7, 11.4]
2011/2012	0 [0, 0]	0.45 [0.42, 0.48]	1.4 [1.4, 1.5]	1.6 [1.5, 1.7]	6.7 [6.4, 6.9]	30.6 [29.5, 31.6]
2012/2013	0.29 [0.27, 0.32]	2.5 [2.4, 2.6]	2.4 [2.3, 2.5]	0.55 [0.51, 0.59]	17.9 [17.4, 18.5]	65.3 [63.8, 67.2]

**Supplementary Table 4.4: Competing risks versus Kaplan-Meier using circulatory/respiratory mortality, the Netherlands, seasons 1999/2000 through 2011/2012.** Comparison of age-group specific influenza-attributable YLL90 with YLL based on Kaplan-Meier survival. Influenza-attributable YLL90 was derived using circulatory/respiratory mortality and averaged over seasons 1999/2000 through 2011/2012. Values in square brackets are 95% uncertainty intervals.

Age-group (years)	Influenza-attributable YLL90			Influenza-attributable YLL (Kaplan-Meier survival) <sup>2</sup>		
	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])
60–64	1159	0.53%	145 [124, 167]	1196	0.55%	149 [128, 172]
65–69	1138	0.47%	170 [150, 191]	1208	0.50%	181 [159, 203]
70–74	1693	0.62%	295 [267, 324]	1864	0.69%	324 [293, 356]
75–79	2230	0.86%	483 [445, 520]	2616	1.00%	566 [522, 609]
80–84	2005	1.03%	630 [589, 672]	2652	1.35%	825 [771, 880]
85–89	1077	1.04%	442 [407, 477]	2462	2.27%	988 [913, 1062]
All (60–89)	9302	0.72%	302 [292, 313]	11998	0.93%	387 [374, 400]

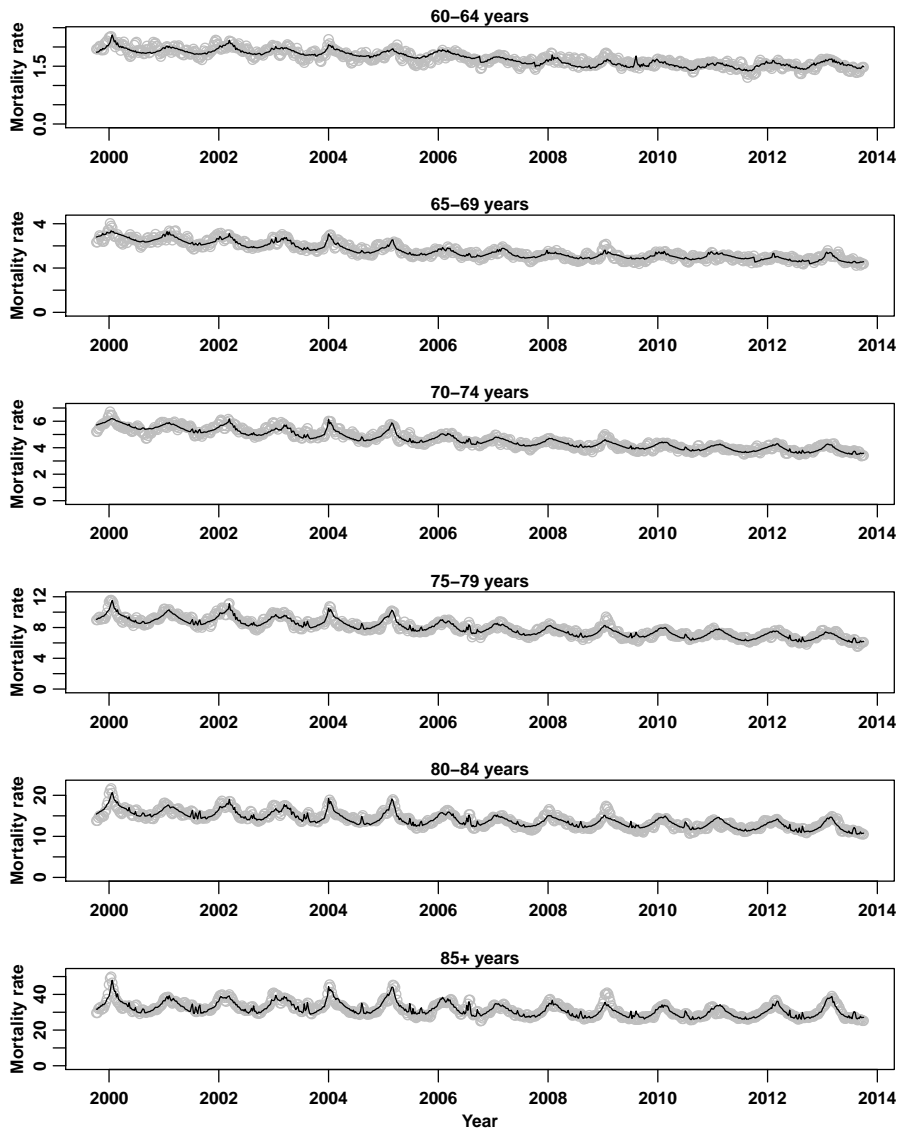
YLL: Years of life lost.

**Supplementary Table 4.5: Competing risks versus Kaplan-Meier using respiratory mortality, the Netherlands, seasons 1999/2000 through 2011/2012.** Comparison of age-group specific influenza-attributable YLL90 with YLL based on Kaplan-Meier survival. Influenza-attributable YLL90 was derived using circulatory/respiratory mortality and averaged over seasons 1999/2000 through 2011/2012. Values in square brackets are 95% uncertainty intervals.

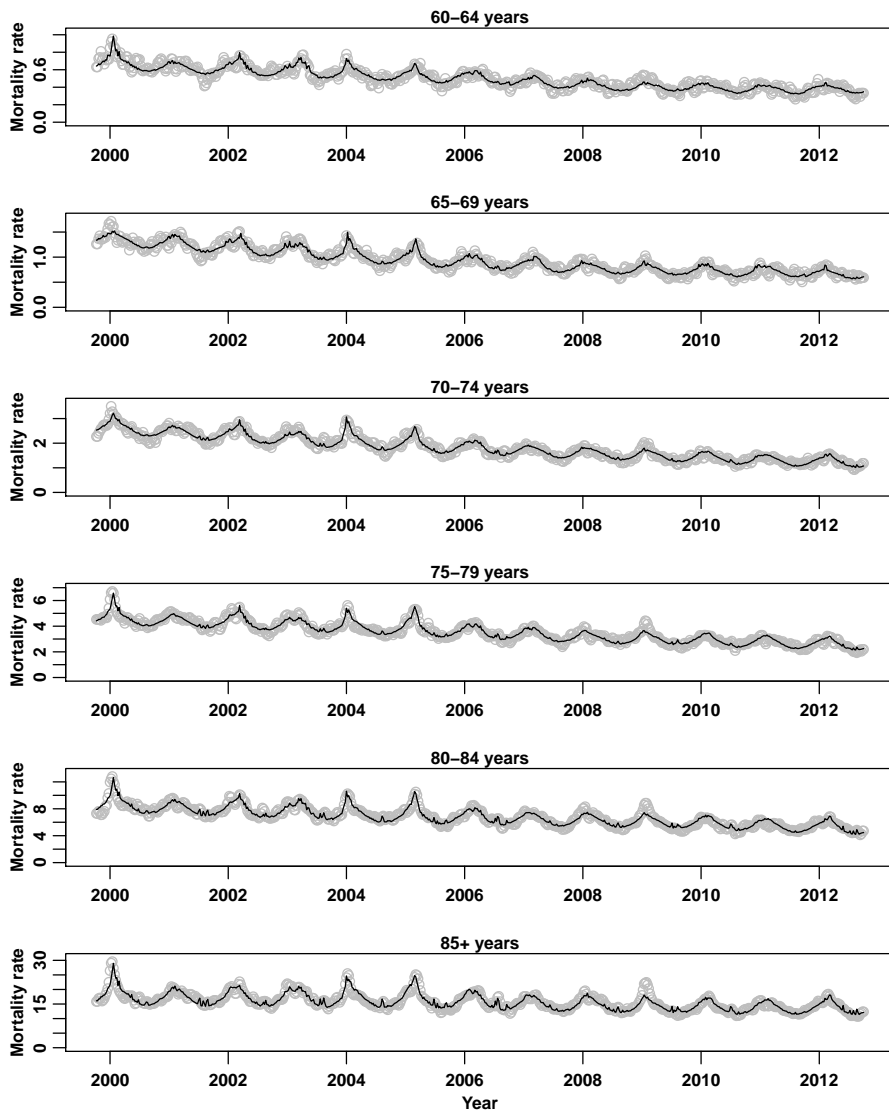
Age-group (years)	Influenza-attributable YLL90			Influenza-attributable YLL (Kaplan-Meier survival) <sup>2</sup>		
	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])
60–64	464	0.22%	59 [42, 77]	478	0.22%	61 [44, 79]
65–69	584	0.24%	87 [65, 111]	619	0.26%	92 [69, 117]
70–74	1088	0.40%	190 [160, 222]	1190	0.44%	207 [175, 243]
75–79	1155	0.45%	249 [214, 285]	1366	0.53%	294 [252, 337]
80–84	1346	0.70%	423 [378, 473]	1798	0.92%	558 [499, 625]
85–89	791	0.76%	325 [286, 367]	1783	1.66%	716 [634, 809]
All (60–89)	5434	0.42%	176 [165, 188]	7245	0.56%	232 [218, 248]

YLL: Years of life lost.

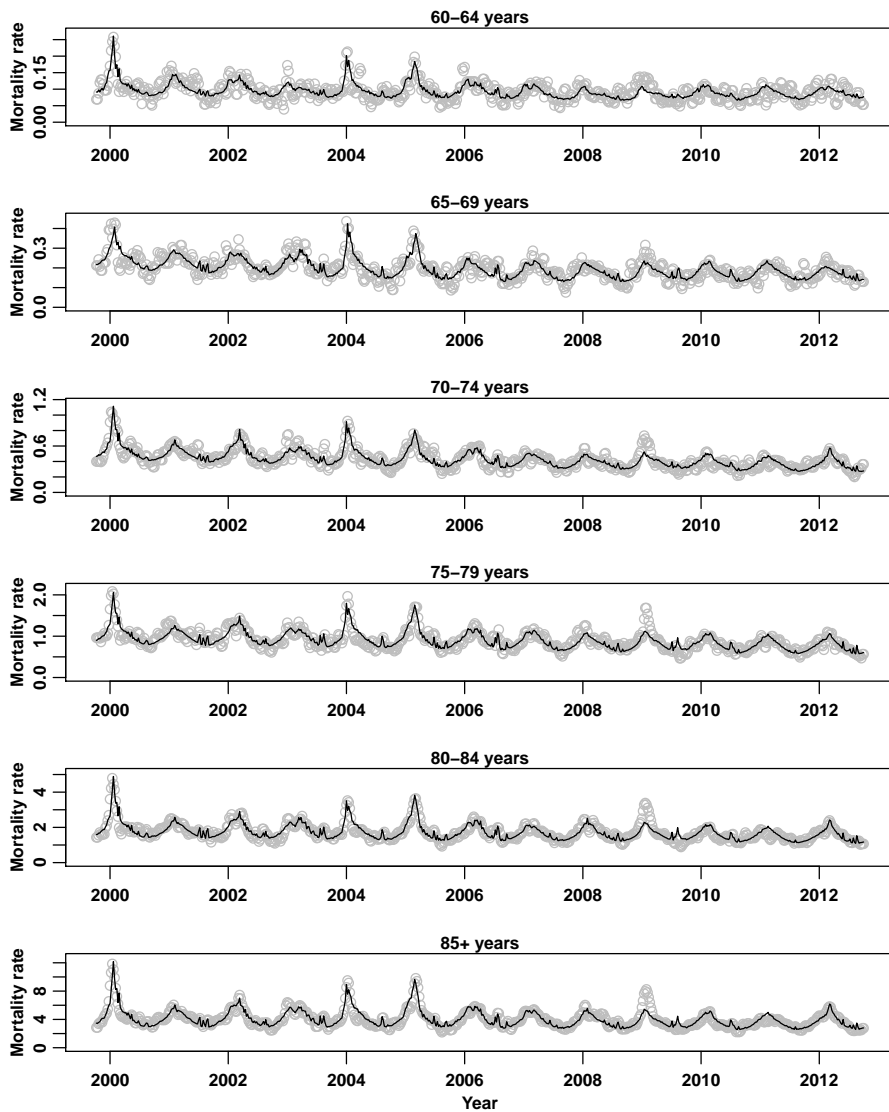




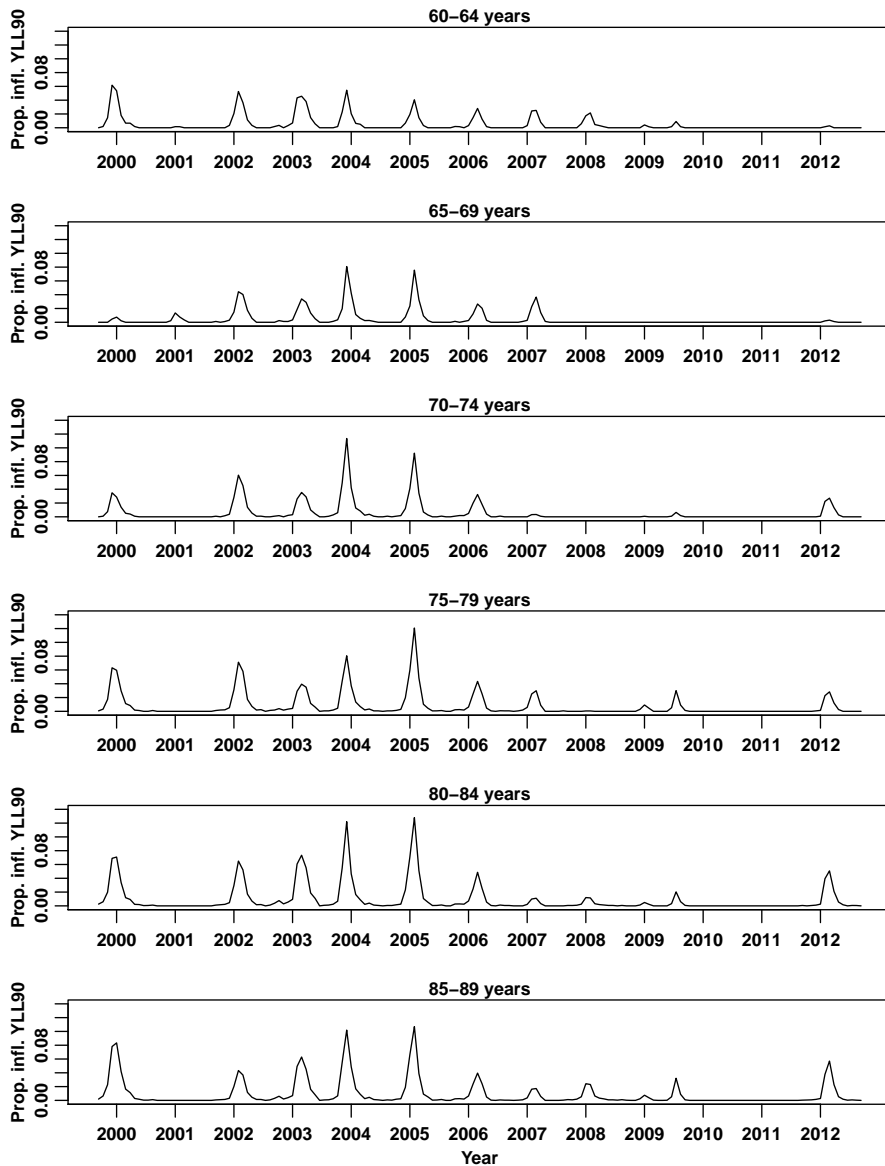
**Supplementary Figure 4.3: Poisson regression model fit to weekly all-cause mortality, the Netherlands, seasons 1999/2000 through 2012/2013.** Mortality rates per 10 000 persons (circles) for each age-group are shown as separate panels. The observed mortality rate data were smoothed using a 3-week moving average.



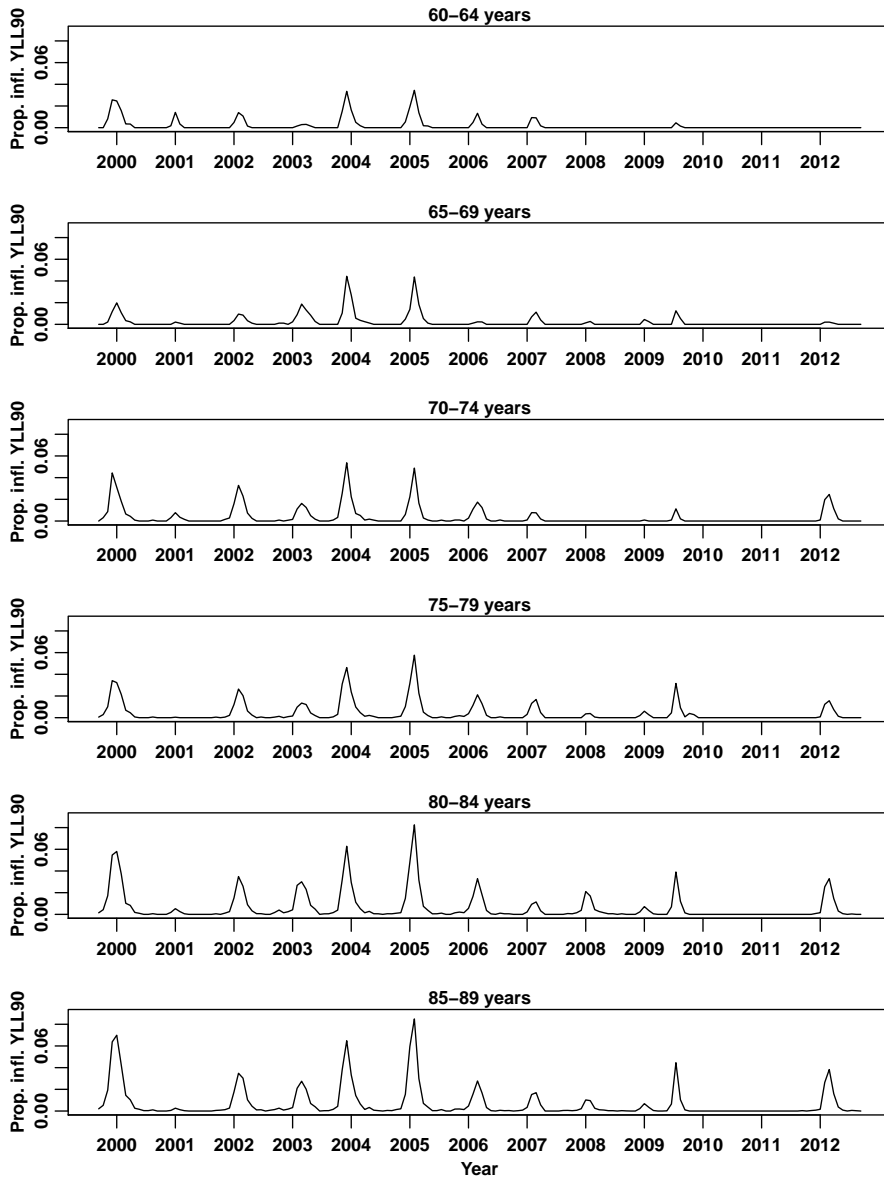
**Supplementary Figure 4.4:** Poisson regression model fit to weekly mortality from a circulatory or respiratory underlying cause, the Netherlands, seasons 1999/2000 through 2012/2013. Mortality rates per 10 000 persons (circles) for each age-group are shown as separate panels. The observed mortality rate data were smoothed using a 3-week moving average.



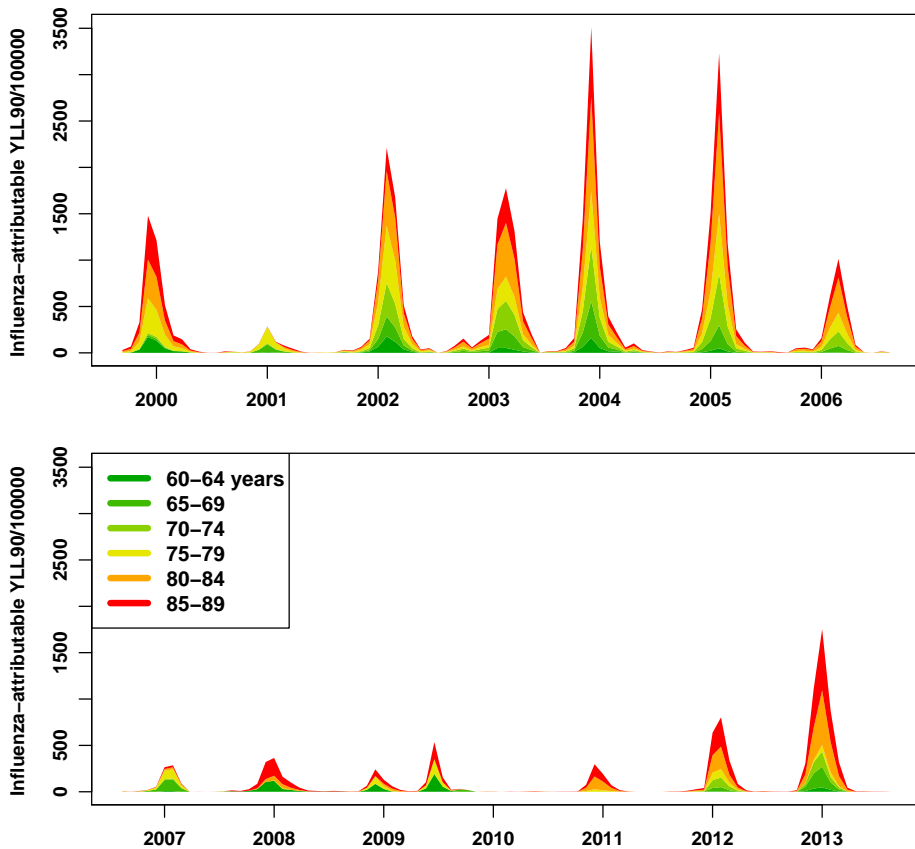
Supplementary Figure 4.5: Poisson regression model fit to weekly mortality from respiratory underlying causes only, the Netherlands, seasons 1999/2000 through 2012/2013. Mortality rates per 10 000 persons (circles) for each age-group are shown as separate panels. The observed mortality rate data were smoothed using a 3-week moving average.



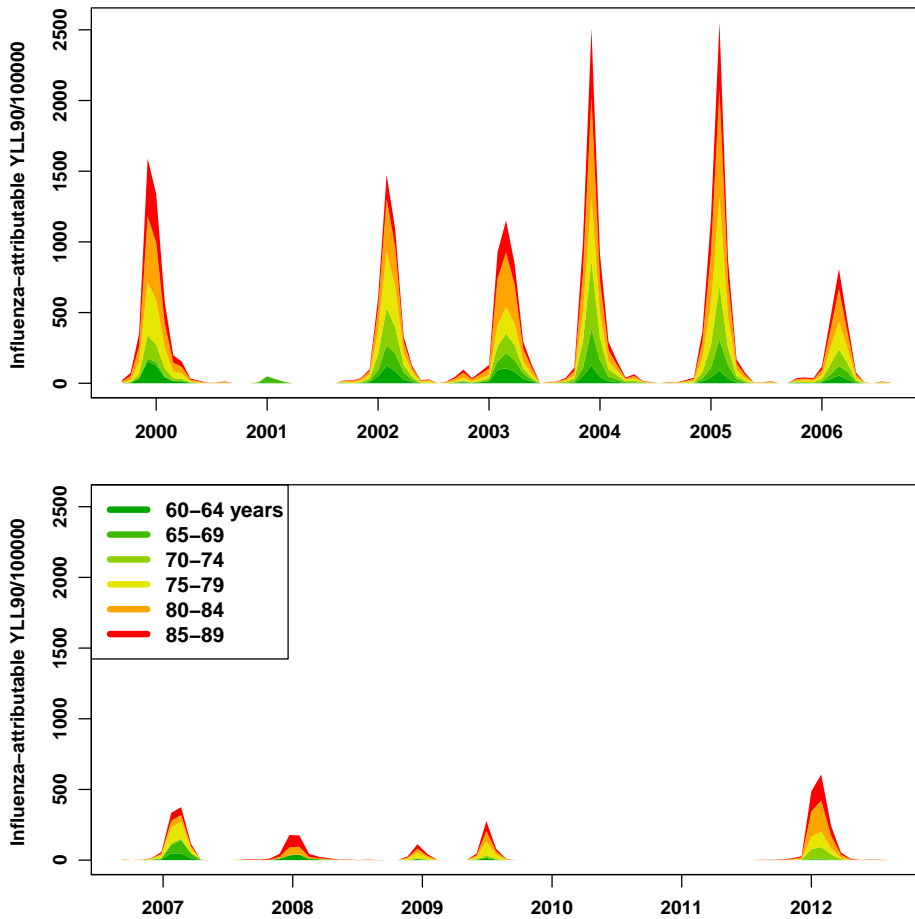
**Supplementary Figure 4.6:** Contribution of influenza to total YLL90 by age-group using mortality from a circulatory or respiratory underlying cause, the Netherlands, seasons 1999/2000 through 2012/2013. Proportion of total YLL90 attributable to influenza aggregated to 4-week intervals for the period 1999/2000 through 2012/2013. Each age-group is shown as a separate panel.



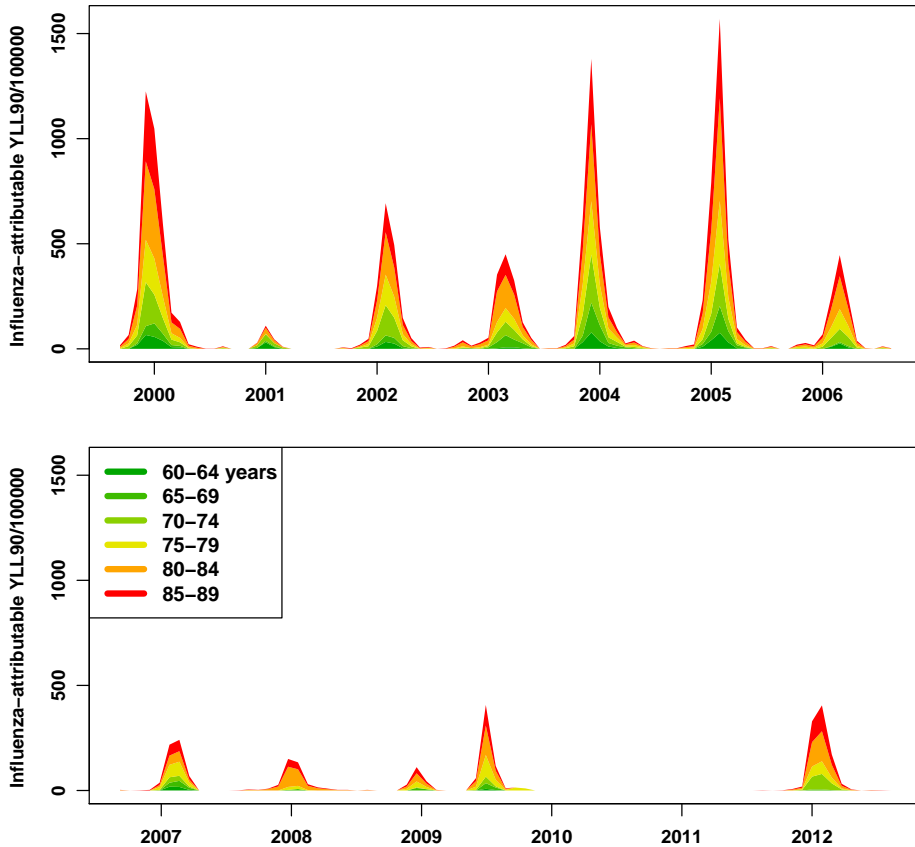
**Supplementary Figure 4.7: Contribution of influenza to total YLL90 by age-group using mortality from respiratory underlying causes only, the Netherlands, seasons 1999/2000 through 2012/2013.** Proportion of total YLL90 attributable to influenza aggregated to 4-week intervals for the period 1999/2000 through 2012/2013. Each age-group is shown as a separate panel.



Supplementary Figure 4.8: Influenza-attributable YLL90 per 100 000 by age-group, the Netherlands, seasons 1999/2000 through 2012/2013. Data is based on all-cause mortality and aggregated over 4-week intervals. Age-group-specific mortality burden is represented as stacked coloured regions.



**Supplementary Figure 4.9: Influenza-attributable YLL90 per 100 000 by age-group using mortality from a circulatory or respiratory underlying cause, the Netherlands, seasons 1999/2000 through 2012/2013.** Data is based on mortality from a circulatory or respiratory underlying cause and aggregated over 4-week intervals. Age-group-specific mortality burden is represented as stacked coloured regions.



Supplementary Figure 4.10: Influenza-attributable YLL90 per 100 000 by age-group using mortality from respiratory underlying causes only, the Netherlands, seasons 1999/2000 through 2012/2013. Data is based on mortality from respiratory underlying causes only and aggregated over 4-week intervals. Age-group-specific mortality burden is represented as stacked coloured regions.



