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Influenza-attributable mortality among the elderly in Switzerland

Estimates and trend assessment for the years 1969–1999

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Summary

Background: Influenza infections are considered responsible for a substantial burden of disease and mortality in the elderly, especially during wintertime. However, death certificates indicating influenza as the cause of death might only partly reflect the mortality attributable to influenza.

Methods: We estimated influenza-attributable mortality for the Swiss resident population of age 60 and older from 1969 to 1999 by Poisson regression modelling of all cause and influenza mortality, and examined long-term trends by age and gender. In sensitivity analyses we additionally used data on official pneumonia deaths, as well as clinical diagnosis of influenza-associated illnesses from the Swiss Sentinel Network.

Results: For the 30 successive respiratory seasons (July of a given year to June of the next year) from 1969/70 to 1998/99 the estimated total number of influenza-attributable deaths in the Swiss population of 60+ was 24 800 (95% confidence interval: 21 000 to 28 600), about 2 times the official count of influenza deaths. Influenza-attributable mortality rate declined from 1969 to 1999, but the yearly number of influenza-attributable deaths nevertheless stabilised at around 600 to 700 in the nineties due to aging of the population. The oldest-aged groups persistently showed the highest influenza mortality rate. Influenza-attributable mortality estimates were substantially higher when using the general practice influenza indicator (by 66%) or the combined cause-of-death category pneumonia and influenza (by 169%).

Conclusions: Only counting official influenza deaths underestimated influenza-attributable mortality in Switzerland by a factor of two to three. Despite a gradual decline in age-specific influenza-attributable mortality rates in the years 1969 to 1999, we estimated an average annual number of 830 deaths in the elderly Swiss resident population. The elderly remain the primary target group for influenza vaccination to reduce influenza-attributable mortality.

Key words: influenza; mortality; time trends; surveillance; Poisson regression

Introduction

Seasonal influenza epidemics are a major public health burden, causing considerable morbidity and mortality worldwide [1, 2]. For the industrialised countries alone, estimates amount to five million cases of severe illness and 250,000 to 500,000 deaths each year [3]. Official death records, with influenza as cause of death, do not fully reflect the actual number of deaths attributable to influenza infections as not all cases are confirmed virologically and, for a large proportion, secondary diseases may follow an acute influenza infection. In particular, influenza has been associated with pneumonia, other respiratory diseases, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus and brain infarction/cerebrovascular disease [4–9]. The influenza-association of deaths resulting from severe secondary complications might be undetected or not recorded [10, 11].

Two main approaches exist to estimate influenza-attributable morbidity or deaths. The traditional, Serfling-type models typically subtract a seasonal, model-generated baseline estimate (for non-epidemic winters) from observed winter deaths [12–14]. Total excess mortality during epidemic weeks is then taken as a measure of the burden of influenza, which usually comprises only a small proportion of total mortality. Excess mortality models require no or only limited external information on seasonal influenza activity, making them indispensable for long-term historical com-

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parisons or for comparisons between countries that differ in method of influenza surveillance [15]. However, as the viral infection takes its toll in non-epidemic years as well, part of the derived baseline mortality is actually influenza-based, leading inherently to an underestimation of influenza-attributable mortality. Other models aim to overcome this problem by dynamically modelling seasonal as well as long-term trends in morbidity or all-cause (or disease-related) mortality using a factor indicating influenza activity [10, 16]. Such models also allow the joint modelling of group- or individual-based risk factors.

Elderly people are a major risk group, that have markedly increased hospital admission [16–19] and mortality rates during influenza epidemics [10, 14, 17, 18]. The aim of this study was to analyse official mortality and population data of those aged 60 years and older to estimate influenza-attributable mortality in Switzerland over three decades, using data from both death records and general practice consultations.

Methods

Data on all-cause and disease-related mortality

From the Swiss Federal Statistical Office we obtained population size and mortality counts of the Swiss resident population for the years 1969 to 1999. All mortality counts were stratified by calendar year, month, sex (male, female), and five-year-age groups (60–64, 65–69, 70–74, 75–79, 80–84, 85+). Denominator counts were stratified by calendar year, sex and five-year age-groups. Mortality counts were provided separately for all causes and for influenza as the cause of death (International Classification of Diseases (ICD) [20] 8th revision codes 470–474 up to 1994 and 10th revision codes J10–J11 for 1995 to 1999, and for pneumonia (ICD-8 codes 480–486 or ICD-10 codes J12–J18). We here denote the cause-of-death category influenza as "official influenza deaths".

General practice consultation data

Since June 1987 the Swiss Federal Office of Public Health has collected general practice (GP) consultation data for influenza-like illness (ILI) in Switzerland as part of the Swiss Sentinel Surveillance Network (http://www.bag.admin.ch/sentinella). The definition used in the Sentinel Surveillance Network for ILI is a respiratory illness with fever above 38 °C, general weakness and myalgia or generalised pain with optional symptoms of cough, rhinitis or arthralgia. Clinical morbidity data are derived from 150 to 250 general practitioners, internists and paediatricians in private practices, who voluntarily report on a weekly basis individual characteristics of patients with a new diagnosis of influenza-like illness according to standard clinical criteria and the total number of consultations. This is used to calculate the weekly proportion of influenza-like illnesses of all consultations and serves as an epidemiological indicator for the influenza activity in the Swiss population. In a proportion of cases, Sentinel-practitioners take swabs on patients with influenza-like symptoms and send these to the Swiss National Influenza Centre for virus detection. For this study we used the mean monthly age- and sex-specific ILI-rates from January 1988 onwards, defined as the proportion of all doctor visits concerning ILI in each sex and age group stratum.

Statistical data analysis

The data set used for the analyses consisted of one record for each calendar year and month and for each age-group (60–64, 65–69, 70–74, 75–79, 80–84, 85+) of men and women, resulting in overall 4464 records for the years 1969 to 1999. Each record contained the count of the total population, and the mortality counts for Switzerland for all cause mortality, official influenza deaths, and official deaths of pneumonia. Stratum-specific ILI-data were available for the years 1988 to 1999 only.

Estimation of influenza-attributable deaths

The aim of our analysis was to estimate the number of deaths attributable to seasonal influenza activity for each calendar year, month, sex and age group stratum. To separate the impact of influenza activity from that of other seasonal factors for mortality, we used a multivariable approach similar to the one used by Thompson et al. [10].

In a first step we calculated, for each stratum, the difference of the number of all deaths (denoted by Y_{tot}) and the number of official influenza deaths (denoted by Y_{flu}). In a second step we modelled the difference Y_{tot}–Y_{flu} in each stratum using multivariable Poisson regression models. We thus estimated the number of influenza-attributable deaths among non-influenza deaths as predicted by the influenza indicator in the model, which was adjusted for the effects of year, general background seasonality, age and sex.

We used a flexible family of Poisson regression models with logarithmic link function and the logarithm of the population size as an offset variable, which allowed us to account for changes in the size of the denominator population. Furthermore we adjusted in a flexible way for age, sex, calendar time and seasonality by incorporating indicator variables for the age groups, for being female and by allowing for linear and quadratic time trends over calendar years and periodic seasonality within a calendar year (sine and cosine functions with periodicity of 12 and 6 months). The formula box represents, for each stratum, the algebraic relationship of the parameters and the variables used. To avoid too many indices we omitted the index

Model formula:

$$
\begin{aligned}
\ln (Y_{tot} - Y_{flu}) = {} & \ln (\text{population size}) + \beta_0 + \beta_1 [\text{year}] + \beta_2 [\text{year}^2] + && \text{(mortality trends)}\\
& \beta_3 [\sin (2\pi \cdot \text{month}/12)] + \beta_4 [\sin (4\pi \cdot \text{month}/12)] + && \text{(seasonality)}\\
& \beta_5 [\cos (2\pi \cdot \text{month}/12)] + \beta_6 [\cos (4\pi \cdot \text{month}/12)] + && \text{(seasonality)}\\
& \beta_7 [\text{sex}] + && \text{(sex)}\\
& \sum_k (\beta_{8k}\, \text{agegroup}_k) + && \text{(age)}\\
& \sum_l (\beta_{9l}\, \text{agegroup}_l \cdot \text{sex}) + && \text{(sex-age interaction)}\\
& \beta_{10} [\text{influenza}] && \text{(influenza indicator)}
\end{aligned}
$$

denoting the individual record records of the data set (year, month, sex and age group stratum).

The main parameter of interest in this model was β_{10}. This parameter represents by how much the monthly stratum specific logarithm of the count $Y_{tot} - Y_{flu}$ increases by one-unit in the chosen indicator for influenza activity in the same month, conditional on the values of all other variables in the model.

For each month in a given calendar year, and for each sex and age stratum, we finally calculated two numbers from the fitted model. First, the predicted total count of deaths, and second, the predicted death count if the influenza activity would have been zero in that month. By taking the difference of these two counts and adding it to the number of official influenza deaths we obtained an estimate of the total number of influenza-attributable deaths. Obviously, the sum of these two counts was always larger than the stratum-specific monthly number of official influenza deaths and was equal to it if the stratum-specific monthly influenza indicator was zero. We thus assumed that the official number influenza deaths serves as a minimal estimate of influenza-attributable mortality.

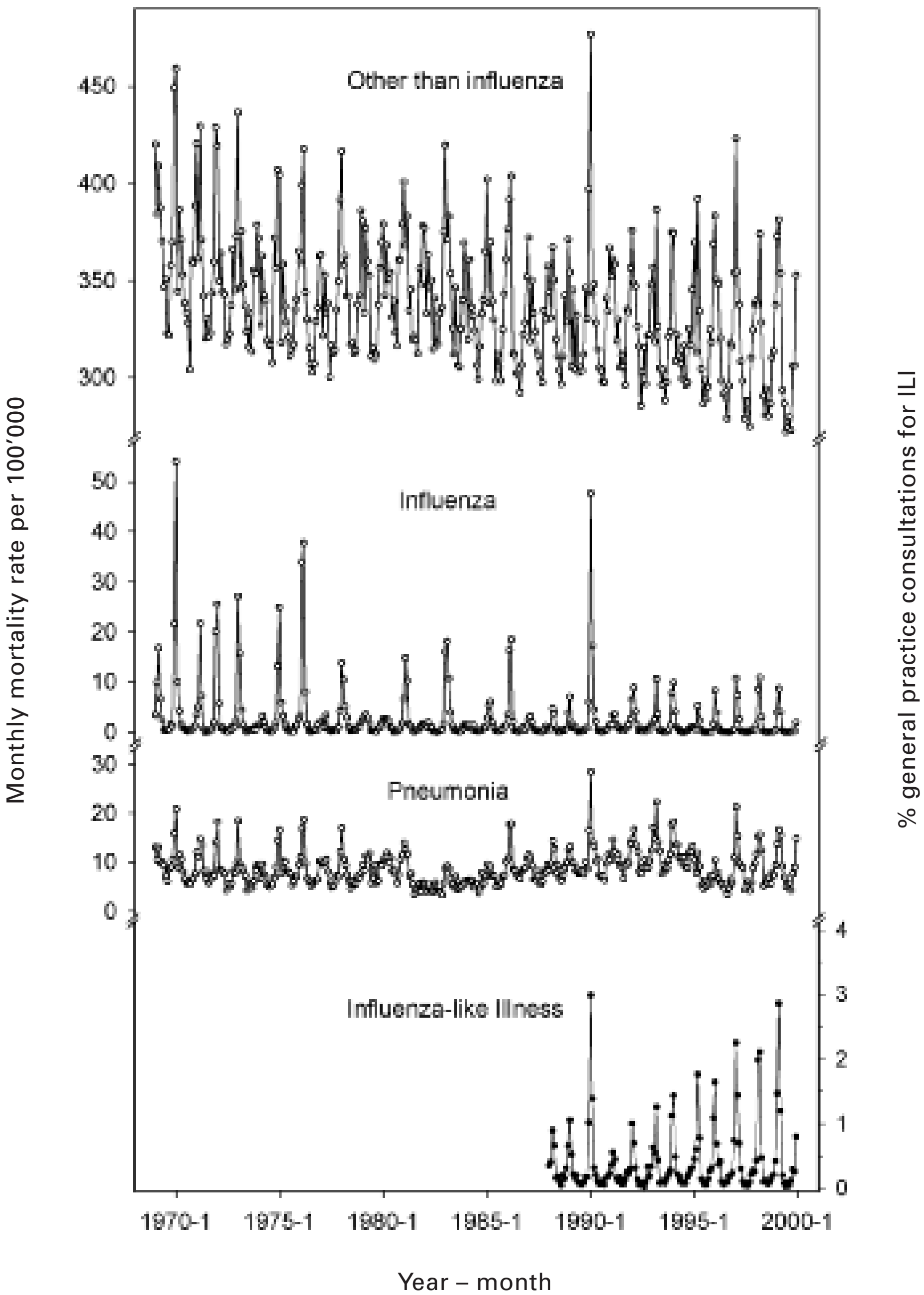
By taking the sum over all sex and age strata and the 12 months from July of a given calendar year to June of the following year we obtained estimates of total deaths attributable to influenza for successive respiratory seasons. We calculated 95% confidence intervals for the estimates of influenza-attributable by the bootstrap method, ie by resampling with replacement from the original data set (12*6*2 = 144 records per 12 month interval) and by repeating the whole estimation process on 300 bootstrap samples [21].

We also explored sensitivity of results to the choice of the influenza indicator used in the regression approach. In the main analysis we used the official influenza mortality rate (monthly counts divided by the denominator population), and refer to this model as the influenza model. In a second model, the P&I model, we used the combined cause-of-death category pneumonia and influenza (P&I) to calculate P&I mortality rate (monthly sum of all P&I deaths divided by the denominator population). In a third model, the ILI-model we used the Sentinel ILI-indicator. Note that this indicator was available for the years 1988 to 1999 only.

In the text we report rounded results (to the nearest 10 for yearly estimates and to the nearest 100 for estimates over several years).

Figure1

Monthly mortality rates for all cause mortality excluding official influenza deaths, influenza mortality, pneumonia mortality (open symbols) and monthly proportion of general practice consultations for influenza-like illness (ILI) from the Swiss Sentinel Surveillance System, for Switzerland and the population of age 60 and older, 1969–1999.



3.2. Investigating the long-term trends in influenza-attributable mortality

To investigate long-term trends in influenza-attributable mortality we calculated for each respiratory season the total influenza-attributable mortality (Y_{totflu}) by age and sex strata as predicted by the influenza model. These season and stratum specific estimates in (Y_{totflu}) were then analysed using Poisson regression with the corresponding population size as an offset variable. We further accounted for the variance in Y_{totflu}, by taking the inverse of the respective relative variances in Y_{totflu} as analytical weights. Predictor variables included year and year square, sex, age, and their mutual interaction.

Data analyses were performed using the STATA 8.2 statistical package [22]. The usual assumption in statistical analyses of independent observations was not fulfilled in this data set, as monthly mortality counts for men and women of a given age group were positively correlated. We therefore used for the calculations of p-values the robust Huber-White sandwich estimator of variance [23, 24].

Results

In Switzerland, monthly mortality rates (deaths per 100,000 persons) for the population aged 60+ showed marked seasonal variation in influenza-mortality as well as in all cause mortality (figure 1). Peaks in influenza mortality typically occurred during the winter months (December-March) with coincident peaks in all cause mortality excluding influenza deaths (the difference of all

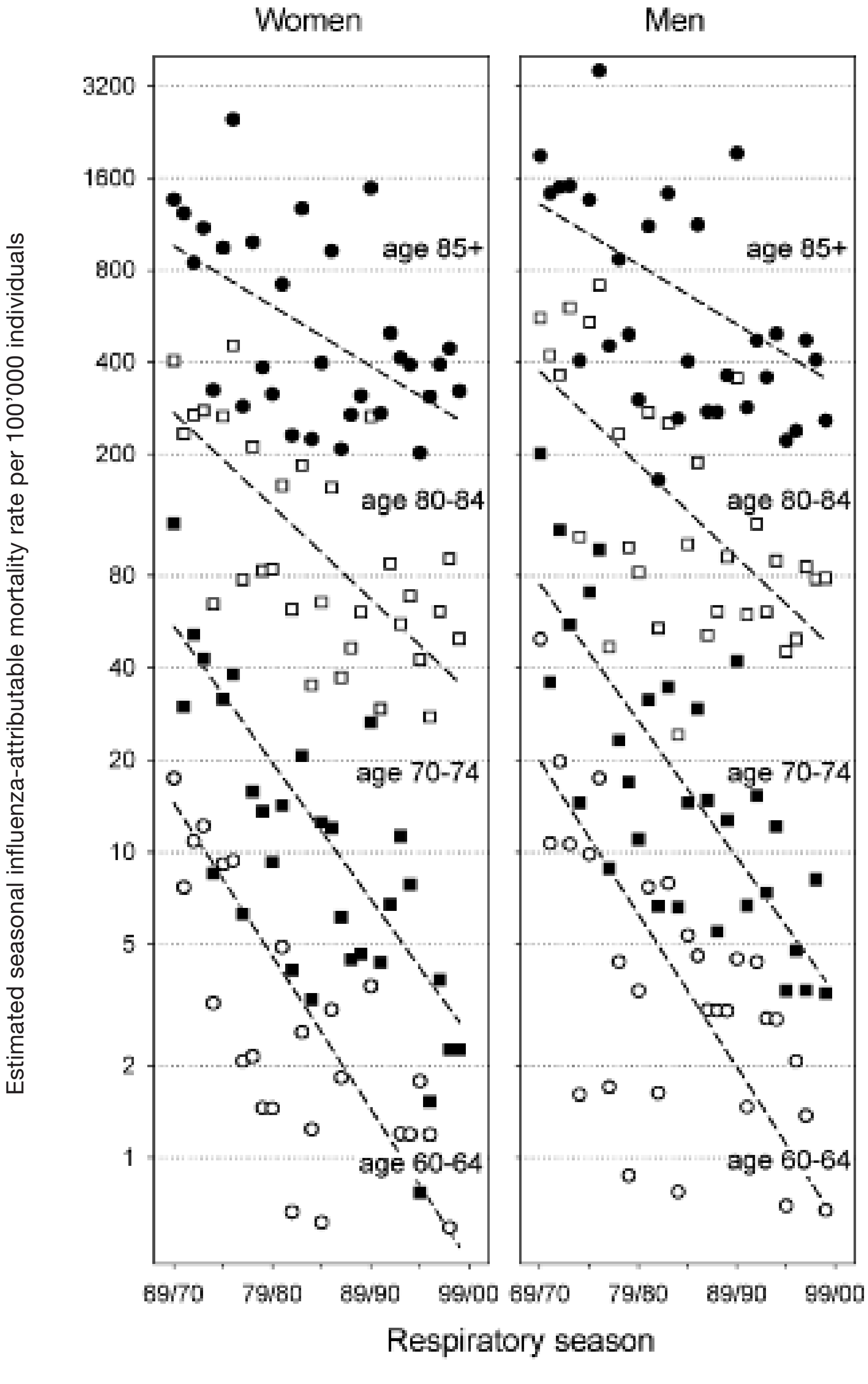


Figure 2

Long-term decline in total estimated seasonal (from June to July of next year) influenza-attributable mortality rate by sex and age group. The symbols give the estimates obtained from the influenza mortality model; the broken lines the predictions obtained from the long-term trend model. Note the logarithmic y-scale, and that the estimates for the two intermediate age groups 65–69 and 75–79 were not plotted for reasons of clarity.

Table 1

Total annual number of recorded official and estimated influenza-attributable deaths in the Swiss age 60+-population over the years 1969 until 1999. Recorded (Rec.) and estimated (Est.) influenza deaths are for both sexes combined. Estimates are based on the influenza mortality model. 95% CI's were obtained by bootstrapping.

Respiratory season	Overall (Age 60+)				Age 60–69		Age 70–79		Age 80+	
	Population size *	Rec.	Est.	95% CI	Rec.	Est.	Rec.	Est.	Rec.	Est.
69–70	1014282.5	992	1864	1209–2529	239	295	429	664	324	906
70–71	1033858.5	431	963	572–1703	45	54	125	187	261	722
71–72	1053361	605	1186	742–1704	102	125	261	404	242	657
72–73	1073435	597	1242	820–1785	82	99	206	316	309	828
73–74	1092324.5	151	314	214–442	14	16	52	78	85	219
74–75	1107206.5	597	1217	853–1833	68	82	219	332	310	803
75–76	1116685	1017	2340	1340–3320	88	103	264	393	665	1843
76–77	1124803.5	148	308	200–417	15	18	39	58	94	233
77–78	1132634.5	456	963	559–1475	30	35	139	208	287	719
78–79	1141070.5	221	448	317–629	19	22	69	100	133	325
79–80	1154326.5	181	361	250–500	16	18	49	70	116	272
80–81	1171995.5	452	948	627–1489	40	48	111	162	301	739
81–82	1189508.5	135	269	177–386	8	9	36	52	91	207
82–83	1205024.5	649	1413	740–2447	48	56	139	200	462	1157
83–84	1220000.5	121	255	175–376	6	7	27	38	88	210
84–85	1235351	253	515	315–849	17	20	62	87	174	409
85–86	1250006.5	565	1216	581–2107	31	36	110	156	424	1024
86–87	1264006	160	322	206–447	13	15	38	52	109	255
87–88	1277712.5	175	367	220–632	7	8	27	38	141	321
88–89	1291739	227	480	264–844	7	8	39	55	181	417
89–90	1305669	1059	2363	1036–4393	47	54	179	253	833	2056
90–91	1319474.5	198	412	253–634	4	5	41	57	153	351
91–92	1333214.5	380	788	508–1361	25	29	48	66	307	693
92–93	1347024	309	635	345–1209	14	16	52	71	243	549
93–94	1362096	349	728	332–1152	17	20	59	82	273	626
94–95	1377298.5	177	363	192–587	7	8	20	28	150	327
95–96	1391142.5	219	472	206–998	7	8	27	38	185	426
96–97	1403830.5	318	695	308–1534	7	8	24	33	287	654
97–98	1417721	363	764	354–1595	5	6	33	45	325	714
98–99	1434098	260	549	234–1055	3	3	27	38	230	508
1969–99	–	11765	24759	21027–28559	1031	1230	2951	4360	7783	19170

* The average of the population size of the two calendar years that contribute the months to the definition of respiratory season.

deaths minus official influenza deaths per 100,000 population). Monthly mortality pneumonia rates also exhibited winter peaks, typically coinciding with the monthly peaks in influenza mortality.

In the main analysis using influenza mortality as the influenza activity indicator, the total number of influenza-attributable deaths in the Swiss population aged 60+ for the respiratory seasons 1969/70 to 1998/99 was 24,800 (95% confidence interval (CI): 21,000–28,600) (table 1). This estimate is about 2.1 (95% CI: 1.8–2.4) times the total number of official influenza deaths, corresponding to an average number of 825 (range 270–2360) influenza-attributable deaths per respiratory season. The highest estimates were obtained for the respiratory seasons 1975/76 and 1989/90. In the nineties (years 1991–1999) the total yearly number of influenza-attributable deaths stabilised at approximately 600 to 700 deaths.

The ratio of the estimated influenza-attributable mortality to recorded influenza deaths over the three decades was similar for both genders, ie 2.2 (95% CI: 1.8–2.5) for men and 2.1 (95% CI: 1.7–2.6) for women. In addition, the ratio was higher in higher age groups, that is 1.2 (95% CI: 0.9–1.4) in persons aged 60–69, 1.5 (95% CI: 1.2–1.7), in persons aged 70–79, and 2.5 (95% CI: 2.0–2.9) in the 80 and older age group (table 1).

Older age groups consistently showed the highest influenza-attributable mortality. In addition, estimates of mean influenza-attributable mortality rates per respiratory season progressively declined over the three decades, and this decline was steepest for the younger age groups (for interaction term respiratory season * age-group: $\chi^2 = 59.62$, d.f. = 5, $p < 0.0001$). The resulting relative risk reduction over 10 respiratory seasons was 71% (95% CI: 59–79%), 66% (95% CI: 53–76%), 53% (95% CI: 42–63%) and 42% (95% CI: 29–53%) for the age-groups 60–64, 70–74, 80–84 and 85 and older, respectively (figure 2). In addition, in each age-group women had a lower influenza-attributable mortality rate than men, and this was most pronounced among the oldest individuals (for interaction term gender * age-group: $\chi^2 = 18.14$, d.f. = 5, $p < 0.003$; figure 2).

Estimates of the total number of influenza-attributable deaths were sensitive to the choice of in-

Table 2

Total annual number of recorded official and estimated influenza-attributable deaths in the Swiss age 60+-population over the years 1969 until 1999. Recorded (Rec.) and estimated (Est.) influenza deaths are for both sexes combined. Estimates are based on the combined pneumonia and influenza model. 95% CI's were obtained by bootstrapping.

Respiratory season	Overall (Age 60+)				Age 60–69		Age 70–79		Age 80+	
	Population size *	Rec.	Est.	95% CI	Rec.	Est.	Rec.	Est.	Rec.	Est.
69–70	1014282.5	992	2835	1980–3743	239	325	429	824	324	1686
70–71	1033858.5	431	1873	1243–2823	45	80	125	331	261	1462
71–72	1053361	605	2067	1450–2819	102	148	261	545	242	1375
72–73	1073435	597	2098	1557–2922	82	125	206	445	309	1529
73–74	1092324.5	151	1096	808–1537	14	37	52	198	85	862
74–75	1107206.5	597	2168	1615–3005	68	105	219	477	310	1587
75–76	1116685	1017	3246	2180–4331	88	124	264	545	665	2577
76–77	1124803.5	148	1199	835–1630	15	35	39	193	94	971
77–78	1132634.5	456	1842	1122–2524	30	53	139	326	287	1463
78–79	1141070.5	221	1345	940–1819	19	38	69	229	133	1079
79–80	1154326.5	181	1425	1057–1928	16	34	49	208	116	1182
80–81	1171995.5	452	2020	1444–2905	40	59	111	301	301	1661
81–82	1189508.5	135	789	566–1095	8	18	36	118	91	653
82–83	1205024.5	649	2031	1284–3241	48	63	139	266	462	1703
83–84	1220000.5	121	914	692–1364	6	15	27	115	88	784
84–85	1235351	253	1335	911–1870	17	30	62	163	174	1142
85–86	1250006.5	565	2358	1352–3527	31	45	110	270	424	2042
86–87	1264006	160	1361	952–1778	13	26	38	165	109	1170
87–88	1277712.5	175	1510	1008–2233	7	18	27	141	141	1352
88–89	1291739	227	1640	1182–2558	7	17	39	156	181	1467
89–90	1305669	1059	3830	2239–6005	47	66	179	372	833	3393
90–91	1319474.5	198	1706	1236–2363	4	16	41	166	153	1523
91–92	1333214.5	380	2223	1533–3340	25	40	48	166	307	2016
92–93	1347024	309	2290	1426–3459	14	27	52	185	243	2077
93–94	1362096	349	2306	1349–3277	17	29	59	199	273	2078
94–95	1377298.5	177	1667	1013–2295	7	16	20	107	150	1544
95–96	1391142.5	219	1367	865–2135	7	12	27	89	185	1266
96–97	1403830.5	318	1932	1189–3634	7	14	24	109	287	1809
97–98	1417721	363	1975	1227–3360	5	12	33	119	325	1845
98–99	1434098	260	1835	1031–2813	3	10	27	117	230	1709
1969-99	-	11765	56284	49245-64427	1031	1636	2951	7643	7783	47005

* The average of the population size of the two calendar years that contribute the months to the definition of respiratory season.

fluenza activity indicator. Using the combined P&I indicator resulted in estimates of influenza-attributable mortality that were 2.3 times higher than the estimates obtained using the influenza mortality model (table 2). The ratio of the results of these two models increased with increasing age, being 1.3 in the 60 to 69 age group and 2.5 for those 80 years and older.

For the years 1988–1999, peaks in monthly proportions of ILI-consultations during influenza seasons coincided with the peak months in influenza-attributable mortality, but the relative height of the annual peaks was different for the two indicators of influenza activity (figure 1). The total number of recorded influenza deaths for the 60+-population was 3859 and varied considerably by winter season, ranging from 177 to 1059 (table 3). The estimate of the number of influenza-attributable deaths using the Sentinel ILI-model was 17,300 (95% CI: 12,200–23,000), approximately 4.5 times the recorded influenza deaths, and approximately 1.7 the estimates obtained using the influenza mortality model (table 3). The total annual mortality estimates of the two models were similar for the respiratory season 1989/90, while the maximal divergence was found in 1994/95, a season with relatively low influenza activity and mortality (table 3 and figure 1). Estimates from the sentinel ILI-model were substantially lower than those obtained from the P&I model.

Discussion

Our analysis among the population aged 60+ in Switzerland provided estimates of numbers of deaths and mortality rates of influenza-attributable mortality in the years 1969–1999. The estimated mortality rate steadily declined over the three decades, most markedly in the population between 60 and 70 years of age. Due to the increase in the population aged 60+, the estimated number of influenza-attributable

Table 3

Estimates of the total influenza-attributable mortality in the Swiss age 60+-population over the years 1988 until 1999 derived from three different models: the influenza mortality model, the Sentinel ILI model and the combined pneumonia & influenza mortality model. 95% CI's were obtained by bootstrapping.

Respiratory season	Rec.	Sentinel model		Influenza mortality model			Pneumonia & Influenza mortality model		
		Est.	95% CI	Est.	95% CI	Ratio*	Est.	95% CI	Ratio*
88–89	227	1125	789–1698	597	329–1298	1.88	2017	1250–2867	0.56
89–90	1059	2963	1560–4804	3062	1814–5336	0.97	4648	3061–6747	0.64
90–91	198	799	576–1050	511	301–911	1.56	2108	1375–3321	0.38
91–92	380	1153	845–1653	979	573–1685	1.18	2726	1845–4336	0.42
92–93	309	1243	822–1813	789	376–1737	1.58	2834	1747–4841	0.44
93–94	349	1424	923–2196	906	501–1669	1.57	2841	1713–4335	0.5
94–95	177	1338	829–1905	449	241–874	2.98	2073	1349–3039	0.65
95–96	219	1406	974–1984	593	216–1469	2.37	1683	965–2628	0.84
96–97	318	1958	1148–3112	878	335–1866	2.23	2393	1297–4774	0.82
97–98	363	1903	1198–3080	957	371–2111	1.99	2431	1432–4087	0.78
98–99	260	1969	1295–2823	688	274–1479	2.86	2286	1247–3773	0.86
1988–99	3859	17282	12177–23022	10409	7976–13674	1.66	28040	22959–35043	0.62

* estimates from the Sentinel ILI model divided by those of the current model

deaths did not exhibit this clear decline. Over all years, we estimated, on average, a yearly number of influenza-attributable deaths of 830 with a large year-to-year variation. In addition, men had a higher influenza mortality rate than women, especially during the earliest years of the study period and among the oldest age groups.

This study analysed national, population-based data covering the whole of Switzerland. The analysis of data over three decades allowed exploring long-term time trends and sex and age differences in influenza-attributable mortality. There is, however, no gold standard in cause of death attribution and in how to clinically and epidemiologically define whether a death should be counted as influenza-associated. Inherently, one assumes that this death would not have happened (or happened substantially later) if no infection with influenza virus had occurred. Therefore, the extent of influenza-attributable mortality needs to be derived from estimation and modelling exercise. In this study we used a flexible family of Poisson regression models, and we explored in a sensitivity analysis whether and by how much the choice of influenza activity indicator affected the results. Our models showed that indicator choice uncertainty was more important than the remaining statistical uncertainty within a chosen model. We think that recorded influenza deaths reflected relevant influenza activity in the population in a specific but less sensitive way than the clinical indicator from the Swiss Sentinel Network. The latter resulted in higher estimates of influenza-attributable mortality. Assuming that official influenza deaths provide a lower bound for influenza-attributable mortality, the results using the ILI-indicator provide an upper bound being approximately five times the number of official influenza deaths. Therefore, sensitivity to model choice can be seen as reflection of the inherent problems to define what is meant by influenza-attributable mortality.

We also acknowledge that our estimation procedure may have been limited by not including more specific indicators of influenza activity, such as time series that reflect the influenza virus type and the magnitude of influenza virus circulation in the population (cf. Thompson et al. [25]). On the other hand, the variation in official influenza death counts may partly capture the variation in virulence as well as prevalence of circulating strains between respiratory seasons. Moreover, while detailed virological data were available for the most recent years only, the use of official influenza death counts allowed us to investigate trends in influenza mortality over three decades.

A legitimate concern regarding our analysis of long-term time trends of the estimates of influenza-attributable mortality rates is the possibility that the results were a modelling artefact. We addressed this by analyzing the official sex and age specific influenza mortality rates. This analysis showed similar long-term trends: the reduction in the official influenza mortality rate over a 10-year period was 71% (95% CI: 67–71%), 68% (95% CI: 65–70%), 49% (95% CI: 46–52%) and 36% (95% CI: 33–38%) for the age-groups 60–64, 70–74, 80–84 and 85 and older, respectively. Therefore, the here reported long-term decline in influenza-attributable mortality reflects the trends in the original data and are not primarily the outcomes of the modelling procedure. It remains possible that the decline reflects a progressive decrease in code use for influenza as primary cause of death on death certificates. However, we consider this unlikely, as the policy for coding and collection of death certificates by the Swiss Federal Statistical Office was essentially unchanged over most of the study period (ie steadfast use of ICD-8 codes from 1969 to 1994).

Our estimates of influenza-attributable mortality and to which extend this mortality is underestimated using official influenza death records are comparable to those estimated for other populations despite the fact that different studies used different time periods, predictors for influenza activity, as well as different statistical modelling techniques. The global ratio of estimated influenza-attributable mortality over recorded mortality was for instance 2.6 in the Netherlands [17], 6.0 in England [26], and 2.0 in Germany [27]. Depending on the choice of influenza activity indicator, our Swiss estimates ranged from 2.1 (flu mortality model) to 4.8 (P&I model), with the Sentinel ILI-model giving intermediate estimates. This was expected, as official influenza deaths likely reflect influenza activity or influenza virulence, which causes mortality, more specifically than the ILI- or the P&I indicator. In particular, the clinical definition of influenza-like-illness does not exclude viral or non-viral pathogens other than influenza that may circulate during winter months as well [10]. Similarly, the higher estimates obtained using the P&I indicator were not surprising, as official pneumonia mortality rate in the elderly was continuously above zero, even in summer months without known influenza activity (see figure 1).

We also compared our result to those obtained by Egger et al. [14], who used excess mortality during defined influenza epidemic weeks to assess influenza-attributable mortality among the elderly in Switzerland over the years 1969 to 1985. For the twelve respiratory seasons with defined epidemic weeks identified, Egger et al. [14] estimated the total number of excess death at 12 202. Fitting the influenza model with Poisson regression and including the same epidemic seasons, we estimated 13 600 (95% CI: 11 300–15 600) influenza deaths, which is approximately 11% higher. Nevertheless, including a further 1773 deaths for the remaining five non-epidemic years (ie 1973/74, 1976/77, 1978/79, 1979/80, 1983/84), we estimated a total of 15 300 (95% CI: 13 000–17 500) influenza-attributable deaths over the complete time period studied by Egger et al. [14]. This suggests that the epidemic-restricted excess mortality method may have underestimated the overall death toll by influenza among the Swiss elderly by about 20%.

Studies in other populations also found a strong increase in influenza-attributable mortality with age among the elderly. For the Netherlands Sprenger et al. [17] estimated 82 and 280 deaths annually per 100,000 persons for people aged 60–69 and people aged 80+, respectively, representing a more than three-times increase in risk. Thompson et al. [10] estimated for the USA that the persons aged 85 or older were 30 times more likely to die of an influenza-attributable all-cause death as compared to persons aged 65–69 years. For Switzerland, and taking persons aged 60–65 as a reference, we estimated the incidence rate ratios for influenza-attributable mortality at 2, 5, 12, 34, and 175 for persons aged 65–69, aged 70–74, aged 75–79, aged 80–85, and 85+, respectively.

Over the 30-year study period influenza-attributable mortality rate steadily declined among people aged 60+ in Switzerland. Similar long-term declines have been observed in other high-income countries, such as the Netherlands [28, 29] and the UK [26] which lead to discussions about the correct methodology for estimation [30]. Contradictory with the Swiss results, an influenza study set in the USA [5] evidenced a decline in the decade following the 1968 influenza pandemic only, while the same research team reported a stabilisation in influenza-related mortality during the 1980s and 1990s [31]. The described decline in influenza-attributable mortality rate in other countries may partly reflect the achievement of recent influenza vaccination campaigns, which presumably reduce morbidity and mortality among the elderly [32–38]. As in other high-income countries, Swiss public health organisations officially recommend and reimburse influenza vaccination for vulnerable groups since 1996. As a result the uptake of influenza vaccination among the elderly has progressively increased over recent years, reaching a vaccination coverage of 40% and 48% in 1998 [39] and 2001 [40]. The variation in the reduction of influenza-attributable mortality also fits the reported lesser effectiveness of influenza vaccination with increasing age [35, 41, 42] and among men than among women [35, 43].

It is important to note however, that the decline in influenza-attributable mortality rate in Switzerland and other high-income countries [26, 29] typically started before the increase in vaccination coverage among the elderly. This excludes vaccination as a driving factor for the initial decline in the risk of death to influenza, while its contribution in recent years relative to other causes is undecided. The long-term decline in influenza-attributable mortality rate might principally indicate an increased competence to resist an influenza infection. It seems plausible to attribute this to a general increase in fitness and improved health status among the elderly over the past three decades, as well as to the acquisition of immunity to the emerging A (H3N2) virus after the 1968 pandemic [31].

In conclusion, only counting deaths with influenza as official cause of death will underestimate influenza-attributable mortality in Swiss residents by a factor of at least two to three. Despite a gradual decline in age-specific influenza-attributable mortality rates in the years 1969 to 1999, we estimated an average annual number of 830 deaths in the Swiss resident population of age 60 or older during regular influenza seasons. The elderly thus remain the primary target group of vaccination campaigns to reduce influenza-attributable mortality.

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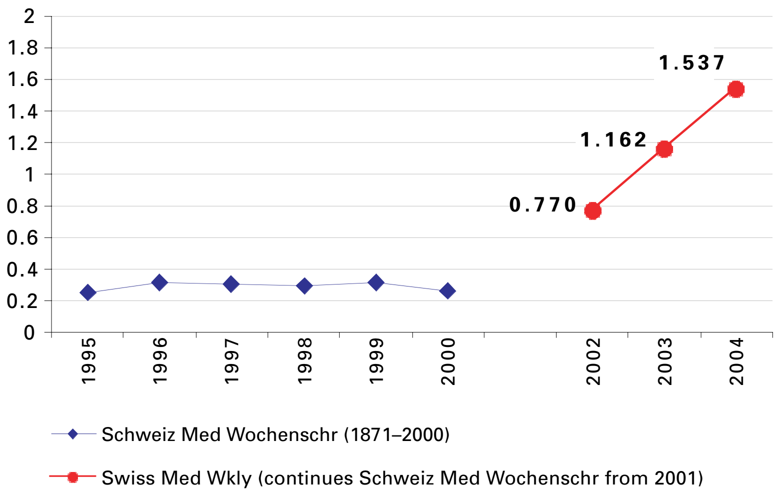

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