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Influenza-related excess mortality, Austria 2001 till 2009

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Influenza-assoziierte Übersterblichkeit, Österreich 2001 bis 2009

Zusammenfassung. Die Influenza-assoziierte Übersterblichkeit wird von öffentlichen Gesundheitsorganisationen für Österreich mit bis zu 6000 Todesfällen pro Grippesaison angegeben, was deutlich über jener von angrenzenden Staaten liegt. Ziel unserer Analyse war eine zuverlässige Schätzung der Influenza-assoziierten Exzessmortalität. Aus der Differenz zwischen beobachteter Gesamtmortalität während einer Influenzasaison und der Mortalität, die in der gleichen Periode ohne erhöhte Influenzaaktivität zu erwarten wäre, wurde die Influenza-assoziierte Exzessmortalität für die Saisonen 2000/2001 bis 2008/2009 berechnet. Die Influenzaktivität wurde mittels Influenzaaktivitätsindex, basierend auf Daten des klinischen Influenza Sentinel-Surveillance-Systems, bestimmt. Die zu erwartende Gesamtmortalität wurde mittels eines zyklischen Regressionsmodells unter Verwendung der wöchentlichen Gesamtmortalitätsdaten von 2000 bis 2009 berechnet. Die Influenza-assoziierte Übersterblichkeit erreichte Höchstwerte in den Saisonen 2002/2003 (1060 Exzess-Todesfälle), 2004/2005 (1102 Exzess-Todesfälle) und 2008/2009 (1192 Exzess-Todesfälle). Der ansteigende Trend im Beobachtungszeitraum von 10 Jahren geht mit einer zunehmenden Alterung der österreichischen Bevölkerung (Anteil der über 65-Jährigen: 2001:15,5 %; 2009: 17,5 %) einher. Unsere Ergebnisse entsprechen Schätzungen der Influenza-assoziierten Übersterblichkeit für Deutschland und der Schweiz. Verlässliche Daten betreffend Exzess-Todesfälle sind eine Voraussetzung für die Erzielung und Erhaltung einer hohen jährlichen Durchimpfung. Die Gültigkeit der derzeit von öffentlichen Gesundheitsorganisationen für Österreich präsentierten Daten betreffend Influenza-assoziierter Übersterblichkeit muss kritisch hinterfragt werden.

Summary. In Austria, a country with a total population of approximately 8.3 million, the published estimates of influenza-associated deaths within the past decade are surprisingly high (up to 6000 deaths per year) when compared to neighbouring countries. The objective of our analysis was to provide reliable estimates of the annual influenza-related deaths in Austria. We estimated the seasonal influenza-related excess mortality by calculating the difference between all-cause mortality observed during the influenza season and the baseline values to be expected during that time span if increased influenza activity was absent. Increased influenza activity was defined as moderate, usual or high, categorized by the influenza activity index using weekly data from the Austrian sentinel clinical surveillance system. For obtaining estimates of baseline all-cause mortality, a cyclic regression model was applied to the time series data on weekly all-cause mortality from 2001 to 2009. Austrian seasonal influenza-related excess mortality peaked in the seasons 2002/2003 (1060 excess deaths), 2004/2005 (1102 excess deaths) and 2008/2009 (1192 excess deaths). The rising trend observed is in parallel with the increasing proportion of the Austrian population older than 65 years for the same time span (2001:15.5%; 2009: 17.5%). Our findings on seasonal influenza-related excess mortality are in accordance with the estimates from Germany and Switzerland, which were derived from a similar approach. In order to gain and to preserve higher compliance with influenza vaccination initiatives, it is essential to have reliable data on influenza-related mortality. Thus, the numbers presented so far by Austrian public health institutions must be challenged.

Key words: Influenza, excess deaths, mortality, surveillance, Austria.

Introduction

Every year, influenza strikes millions of Europeans of all ages. Influenza is a seasonal disease with high epidemic potential, which can be associated with increased mortality in the winter. In Austria, a country with a total population of approximately 8.3 million, the published estimates of seasonal influenza-associated deaths within the past decade are surprisingly high (up to 6000 deaths per year) [1–4] when compared to neighbouring countries. Germany,

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with a total population of approximately 10 times that of Austria, reported estimates of seasonal influenza-associated excess deaths between 0 and 12,000 for the seasons 2000/2001 until 2005/2006 [5]. Switzerland, with a total population of 7.8 million reported 1,324 seasonal influenza-associated excess deaths on average for the period 1969–1985 [6].

In Austria, a sentinel clinical surveillance system for influenza has been in place since 1992 [1]. It consists of a network of general practitioners and pediatricians, who report cases of influenza-like illness (ILI) weekly to the Austrian Reference Centre for Influenza Epidemiology at the Austrian Agency for Health and Food Safety (AGES) during the influenza season. Since 2000, a sentinel virological surveillance system (DINÖ) has been operated by the National Reference Laboratory for Influenza at the Institute of Virology of the Medical University Vienna. A sentinel network of general practitioners sends throat swabs from patients with influenza-like illness to the National Reference Laboratory for Influenza. Another five additional so-called influenza laboratories contribute non-sentinel virological data to the surveillance of influenza. All the clinical and virological data (sentinel and non-sentinel data) are aggregated by the Austrian Reference Centre for Influenza Epidemiology on a weekly basis. This national surveillance data on influenza is reported to the World Health Organization (WHO/ EuroFlu) and the European Centre for Disease Prevention and Control (ECDC).

To our knowledge, Austrian mortality data on influenza have not been reliably analysed so far.

In Austrian mortality statistics, death attributable to influenza is often noted under other causes than influenza. Therefore, the true number of influenza-related deaths is underestimated since official death records rarely state influenza as cause of death. The all-cause mortality is more useful for assessing the impact of influenza on the annual mortality [7]. The objective of our analysis was to provide reliable estimates of the seasonal influenza-related excess mortality in Austria.

Materials and methods

The influenza-related excess mortality was estimated by calculating the difference between observed all-cause mortality during the influenza season and the respective baseline values to be expected in the absence of increased influenza activity. This method was initially introduced by Serfling *et al.* [7] and further developed by Simonson *et al.* [8].

All-cause mortality

Data on all-cause mortality by week of death from 2001 to 2009 were provided by Statistics Austria. We used "Fast Fourier Transform" [9] to identify significant cyclical components in the time-series of all-cause mortality data of 256 weeks from calendar week 1, 2001 to calendar week 47, 2005 which indicated one cyclical component of 52 weeks length. Thereafter, a cyclic regression model (cyclic regression model I) was applied to the time series data on weekly all-cause mortality from 2001 to 2009 described by the equation $Y_t = a + bt + \Sigma R\cos(\omega t + \theta)$; where Y is the expected all-cause mortality, a and b are intercept and slope, respectively, of a linear term, t is the index for week reported death, R is the amplitude of the periodic variation, ω is its frequency and θ is the phase. Ninety percent CI was calculated based on the standard deviation of the residuals according to the formula where t is the expected all-cause mortality in a given week t, Y_O is any mortality observed during the study period, Y_E is any mortality expected in the same week as Y_O, n is the number of observations and dof is the number of degrees of freedom.

$$\hat{Y}_t \pm 1.64 \cdot \sqrt{\frac{\Sigma(Y_O - Y_E)^2}{n - dof}}$$

Influenza activity index

In order to estimate the extent of seasonal influenza activity, the influenza activity index was used [10]. The influenza activity index was conceptualized to uniformly estimate seasonal influenza activity while categorising into low, moderate, usual and high. For determining this index *influenza background activity* and the *reference value for a usual influenza season* are required. *Influenza background activity* was calculated as follows: The mean of the ILI incidence estimates for each specific week from the influenza seasons 1992/1993 to 2008/2009 was calculated. All weeks in which the ILI incidence exceeded the mean value were excluded followed by calculation of the mean of the ILI incidence values of the remaining weeks; this mean was considered to reflect the weekly influenza background activity (i.e. background ILI incidence). The *reference value for a usual influenza season* was determined as follows: The usual influenza season was computed based on 17-year ILI surveillance data (1992/1993-2008/2009). We calculated the mean and the standard deviation of all weekly ILI incidence values from this period. The mean value plus 1.5 times standard deviation was considered as lower limit and the mean plus three times standard deviation as upper limit. An influenza season among the 17 seasons studied with a peak of ILI incidence between the upper and lower limits was considered as a usual influenza season. Ten seasons (1992/1993, 1995/1996, 1996/1997, 1997/1998, 2002/2003, 2003/2004, 2004/2005, 2006/2007, 2007/2008, 2008/2009) having fulfilled this criterion, were selected. Within each of the 10 selected "usual influenza seasons", the ILI incidence of the peak week and those of each calendar week prior and after this peak week (considered as highest influenza activity in the usual influenza season) were selected for calculation of the reference value. The weekly influenza-related excess morbidity was calculated by the observed ILI incidence in these 3 weeks selected minus the background ILI incidence of these three weeks. Finally, the mean of these 30 values of influenza-related excess morbidity gave the reference value for a usual influenza season.

Thus, the influenza activity index for each week of the seasons 2000/2001 until 2008/2009 was calculated as difference between the observed ILI incidence and background ILI incidence for each of the weeks in relation to the reference value for a usual influenza season.

$$\frac{\text{Observed ILI-incidence} - \text{Background ILI-incidence}}{\text{Reference value}}$$

The index discriminates the influenza activity into low (i.e. index: 0–40%), moderate (i.e. index: 41–80%), usual/medium (index: 81–120%) and high activity (index: >120%) [8]. Moderate, usual or high influenza activity was defined as increased activity.

Refitting of the cyclic regression model after omitting any week during which influenza activity was increased as estimated by the influenza activity index and during which observed all-cause mortality exceeded modelled mortality (using the upper limit of the 90% CI of the modelled number of all-cause deaths) (cyclic regression model II) yielded a baseline all-cause mortality, which would be expected in the absence of increased influenza activity.

Computation of the influenza-related excess mortality

The influenza-related excess mortality for the seasons 2001 starting with calendar week 1 until 2008/2009 calendar week 20 was estimated as the sum of all positive weekly excess values (i.e. observed minus expected all-cause mortality) within the weeks of moderate, usual or high influenza activity as indicated by the influenza activity index. In addition to this crude estimate, a more conservative estimate was obtained by subtracting the upper 90% confidence limits instead of the model point estimates from the mortality values observed.

Results

All-cause mortality, 2001–2009

Figure 1 displays the observed and expected weekly all-cause deaths, as estimated by the cyclic regression model

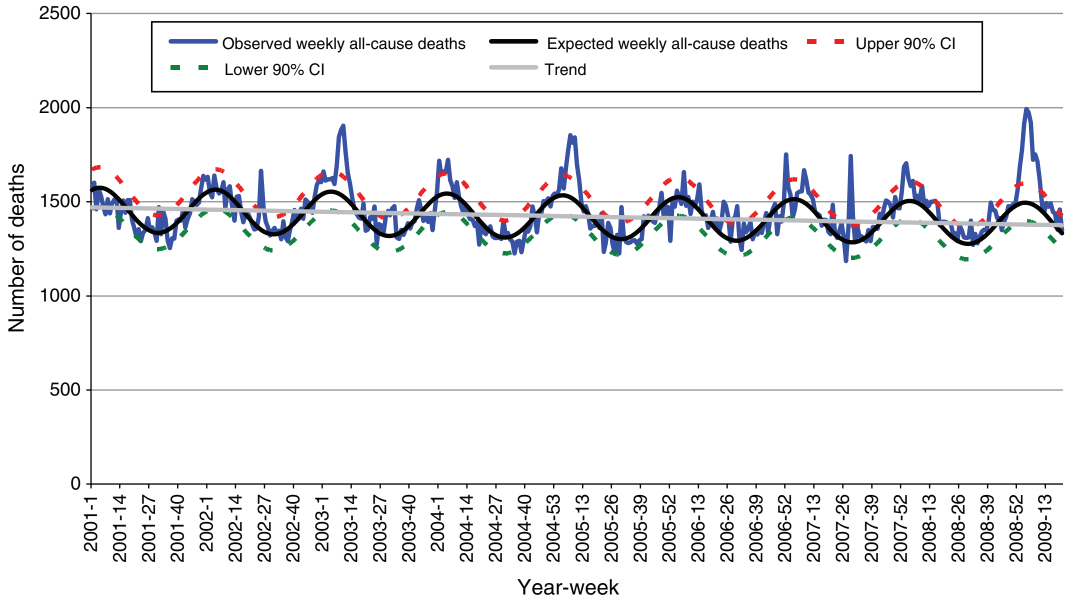

Fig. 1. Observed weekly number of all-cause deaths (blue line) and modelled weekly number of all-cause deaths (black line) as estimated by cyclic regression model I, modelled upper and lower limits of 90% confidence interval (red and green lines), and modelled secular trend of all-cause deaths (grey line); 2001 (calendar week 1) – 2009 (calendar week 13)

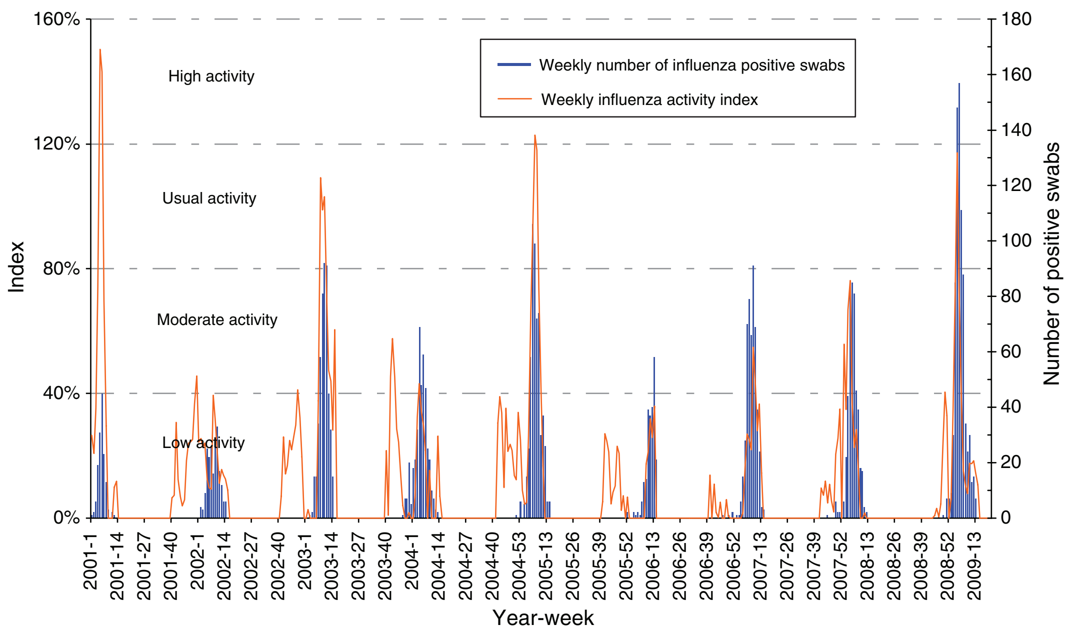

Fig. 2. Seasonal influenza activity categorized by the activity index (low, moderate, usual and high) and the weekly number of influenza positive swabs[1], 2001 (calendar week 1) – 2009 (calendar week 13); [1]source: sentinel virological DINÖ surveillance system of the National Reference Laboratory for Influenza

I (expected all-cause mortality $= e^{(7.28-0.00012t+0.08\cos(2\pi t/52+4.62))}$). The weekly all-cause mortality experienced a slightly decreasing secular trend ($p = 0.037$) and followed a seasonal pattern peaking in the winter weeks between calendar week 40 and calendar week 20 of the next year. From calendar week 1, 2001 until calendar week 20, 2009 the weekly all-cause excess mortality (i.e. observed minus expected values of weekly deaths) ranged between 0 and 497 deaths (0.01–6.04 deaths /100,000 population) with an average weekly excess of 48 deaths (0.59 deaths/100,000 population). During the winter period (calendar weeks 40–20 of the following year), the excess deaths per week averaged 51 (0.62 deaths/100,000 population) (Fig. 1).

Influenza activity index, seasons 2001–2009

Figure 2 displays the seasonal influenza activity categorized by use of the influenza activity index compared with the weekly number of influenza positive swabs derived from the sentinel virological DINÖ surveillance system of the National Reference Laboratory for influenza. The index categorized 2005/2006 as a season with low influenza activity. The seasons 2001/2002, 2003/2004, 2006/2007 and the season 2007/2008 showed moderate influenza activity. A usual influenza activity was observed in the 2002/2003 and 2008/2009 seasons and high influenza activity was seen in the 2000/2001 and 2004/2005 seasons.

Influenza-related excess mortality, seasons 2001–2009

Our findings on the crude and conservative estimates of seasonal influenza-related excess deaths compared with the seasonal distribution of the influenza types and subtypes are displayed in Fig. 3 and summarized in Table 1. The seasonal influenza-related excess mortality peaked in 2002/2003 with 1,060 deaths, in 2004/2005 with 1,102 deaths and in 2008/2009 with 1,192 deaths according to our conservative estimates; in all three seasons the influenza subtype A/H3N2 was dominant. The model yielded no excess deaths related to influenza for the seasons 2000/2001 (concerning calendar week 1–20, 2001 only), 2001/2002 and 2005/2006. For the seasons 2003/2004, 2006/2007 and 2007/2008 45, 59 and 172 influenza-related excess deaths were estimated (Fig. 3, Table 1).

Discussion

The true impact of influenza on the winter excess-mortality is severely underestimated when taking the numbers of deaths attributable to influenza derived from death certificates. Analyses of death certificates show that clinicians often do not attribute influenza-related deaths to influenza, but rather to a pre-existing underlying condition such as cardiovascular events or metabolic disorders [11]. On the other hand, numbers of influenza-related deaths provided by public health authorities severely overestimate the influenza impact on mortality in Austria. Overestimating the influenza-related deaths might be a biased attempt of vaccine advocates to increase influenza vaccine uptake.

Our analysis provides estimates of seasonal influenza-related excess mortality based on inference from seasonal patterns in all-cause death series of weekly data. The method used was cyclic regression modelling yielding baseline all-cause mortality values expected if increased influenza was absent. Increased influenza activity was defined as moderate, usual or high, categorized by the influenza activity index [10]. This index was introduced by Uphoff for harmonising national influenza surveillance morbidity data from the former European influenza surveillance system (EISS) [10]. We computed the reference value for a usual influenza season based on 17-year ILI surveillance data (1992/1993–2008/2009) instead of referring to the national scientists' assessment, as already previously suggested by Uphoff himself [10].

The seasonal influenza-related excess mortality of Austria peaked in the seasons 2002/2003 (1,060 excess deaths), 2004/2005 (1,102 excess deaths) and 2008/2009 (1,192

Table 1. Influenza-related excess mortality as estimated by the re-fitted cyclic regression model compared with the numbers of influenza deaths according to death certificates and the frequency distribution of the seasonal influenza types/subtypes

Influenza season	Influenza deaths acc. to death certificates *n*	Influenza-related excess mortality *n*		Seasonal Influenza type/subtype % *of positive swabs*				
		Crude estimates of excess deaths	Conservative estimates of excess deaths	Influenza A	Influenza B	Influenza A subtyped (*n*)	A/H3N2	A/H1N1
2000/2001*	24	0	0	98%	2%	64	0%	100%
2001/2002	31	71	0	43%	57%	NA	NA	NA
2002/2003	14	1563	1060	90%	10%	NA	100%	0%
2003/2004	0	259	45	100%	0%	395	100%	0%
2004/2005	23	1582	1102	61%	39%	123	66%	34%
2005/2006	10	0	0	73%	27%	139	95%	5%
2006/2007	5	215	59	99%	1%	427	99%	1%
2007/2008	1	410	172	86%	14%	262	0%	100%
2008/2009	16	1455	1192	76%	24%	438	97%	3%

*Data concerning calendar week 1–20, 2001 only; NA: data not available; Sources: Statistics Austria, WHO/ FluNet for data 2000–2003; National Reference Centre for Influenza Epidemiology for data 2004–2009, National Reference Laboratory for Influenza at the Institute of Virology, Medical University, Vienna.

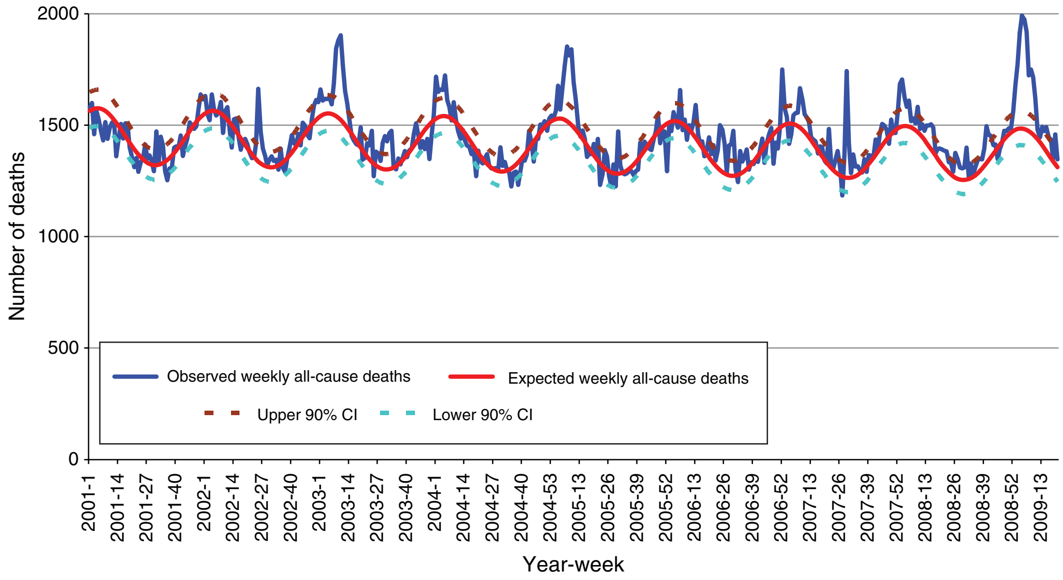

Fig. 3. Observed weekly number of all-cause deaths (blue line), and modelled weekly number of all-cause deaths as expected in the absence of increased influenza activity estimated by cyclic regression model II (red line), modelled upper and lower limits of 90% confidence interval (brown and light blue lines); 2001 (calendar week 1) – 2009 (calendar week 13)

excess deaths). The observed rising trend is in parallel with the increasing proportion of the Austrian population older than 65 years for the same time span (according to Statistics Austria: 2001:15.5%; 2009: 17.5%). Our findings on influenza-related excess deaths are in accordance with estimates per season from Germany and Switzerland, which were derived from a similar approach [6,12,13], and with the estimates from the United States (total population 310 million, estimated annual average of 36,000 deaths attributable to influenza virus infection), which equals 963 excess deaths for a population of 8.3 million [14].

Dushoff [15] recommended that analyses of influenza burden on the mortality rate should also be tied to estimates of laboratory-confirmed influenza cases. Therefore, we re-applied our method by using virological surveillance data instead of ILI data for computing the influenza activity index (data not shown). The data on laboratory confirmed cases of influenza derived from the sentinel virological DINÖ surveillance system of the national reference laboratory for influenza. This second approach would have yielded similar estimates as compared to our first approach using ILI data: the seasonal influenza-related excess mortality would peak also in the seasons 2002/2003 (1,055 excess deaths), 2004/2005 (1,353 excess deaths) and 2008/2009 (1,894 excess deaths), again with an increasing trend (Table 2 summarizes both models). For the seasons 2003/2003, 2005/2006 and 2006/2007 the second approach would yield slightly higher estimates of influenza-related excess deaths compared with findings of the first approach. This might be due to underestimation of true influenza activity by using only clinical surveillance data. However, the resulting numbers do not differ substantially.

Excess mortality due to influenza is frequently used as an important determinant for assessing the severity of epidemics [16]. So far, influenza mortality data have not been reliably incorporated in the routine surveillance of influenza in Austria. In the influenza seasons 2000/2001, 2001/2002 and 2007/2008, for which we found no or only low numbers of influenza-related excess death, influenza A/H1N1 or influenza B was dominant according to the data provided by the National Reference Laboratory for Influenza. Based on findings in Germany, Italy and in the USA [5, 12, 16, 17], the more severe influenza seasons were associated with predominance of A/H3N2. The seasons 2002/2003, 2004/2005 and 2008/2009, for which our analysis yielded highest numbers of excess deaths, was also associated with A/H3N2. The low numbers of influenza

Table 2. Conservative estimates of influenza-related excess deaths based on clinical influenza surveillance data compared with estimates based on virological influenza data[1], 2001/2002–2008/2009

Influenza season	Influenza-related excess mortality	
	Based on virological surveillance data	Based on clinical surveillance data (see *Results*)
	Conservative excess deaths	Conservative excess deaths
2000/2001*	0	0
2001/2002	0	0
2002/2003	1,055	1,060
2003/2004	421	45
2004/2005	1,353	1,102
2005/2006	274	0
2006/2007	543	59
2007/2008	183	172
2008/2009	1,894	1,192

*Data concerning calendar week 1–20, 2001 only; [1]Source: data from the sentinel virological DINÖ surveillance system of the National Reference Laboratory for Influenza.

related deaths in 2003/2004, 2005/2006 and 2006/2007, despite predominance of A/H3N2, might be due to sufficient immunity among the population against this subtype acquired during the previous A/H3N2 dominated seasons. High vaccination coverage is unlikely to explain the low influenza-related morbidity and mortality despite predominance of A/H3N2 in these seasons, as the influenza vaccine uptake is only around 17% in Austria [1, 4].

Our study has limitations as follows: To minimize the likelihood of taking into account deaths which were rather due to winter-related causes other than influenza, we attributed mortality to influenza only if it occurred during weeks with increased influenza activity as indicated by sentinel clinical surveillance data. Another important cause of excess deaths during influenza seasons is respiratory syncytial virus (RSV) infection [18]. Data on RSV activity provided by the Institute of Virology of the Medical University Vienna were available for the seasons 2004/2005 until 2008/2009 (http://www.virologie.meduniwien.ac.at). In the seasons 2005/2006 and 2006/2007 the peak of RSV activity overlapped with the peak of influenza activity. For these two seasons at least, overestimation of the influenza-associated excess mortality cannot be ruled out. Other relevant winter-related causes of deaths such as temperature have been not considered; this might have also caused overestimation of the influenza-related excess deaths.

We modelled the baseline all-cause mortality, which would be expected in the absence of increased influenza activity by removing all weeks with excess all-cause mortality and increased influenza activity. Hereby we may have falsely retained weeks in which influenza-associated mortality was present but no excess deaths occurred; consecutively the modelled baseline values would have been overestimated and the yielded number of influenza-related excess deaths underestimated.

Finally, our estimates are across all age groups since age-specific data on weekly all-cause mortality were not available. Age-specific estimates of influenza-related excess deaths are urgently required. Otherwise, evidence-based targeted public health messages are not possible. People 65 years of age and older are most severely affected. In the U.S. they account for more than 60 percent of influenza-related hospitalizations and 90 percent of deaths [19, 20]. In order to gain and to preserve higher compliance with influenza vaccination initiatives, it is essential to have reliable data on influenza-related mortality [21, 22]. The numbers presented so far by Austrian public health institutions must be challenged.

Conflict of interest
The authors declare that there is no conflict of interest.

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