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INFECTIOUS DISEASES

Attributable deaths due to influenza: a comparative study of seasonal and pandemic influenza

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Abstract Influenza epidemics lead to an increase in hospitalizations and deaths. Up to now the overall impact of attributable deaths due to seasonal and pandemic influenza viruses in Austria has not been investigated in detail. Therefore we compared the number and age distribution of influenza associated deaths during ten influenza epidemic seasons to those observed during the pandemic influenza A(H1N1)2009 season. A Poisson model, relating age and daily deaths to week of influenza season using national mortality and viral surveillance data adjusted for the confounding effect of co-circulating Respiratory Syncytial Virus was used. We estimated an average of 316 influenza associated deaths per seasonal influenza epidemic (1999/2000–2008/2009) and 264 for the pandemic influenza season 2009/2010 in the area of Vienna, Austria. Comparing the mortality data for seasonal and pandemic influenza viruses in different age groups revealed a statistically significant increase in mortality for pandemic A(H1N1)2009 influenza virus in the age groups below 34 years of age and a significant decrease in mortality in those above 55 years. Our data adjusted for co-circulating RSV confirm the different mortality pattern of seasonal and pandemic influenza A(H1N1)2009 virus in different age groups.

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Introduction

Influenza epidemics occur virtually every winter [1, 2] leading to an increase in hospitalizations and deaths especially among the elderly and people with high-risk medical conditions [1–3]. In 2009, a novel influenza virus emerged as the predominant influenza strain in the human population causing the first pandemic in the twenty-first century [4]. Studies on the mortality pattern of this new pandemic influenza A(H1N1)2009 virus showed that the virus primarily affects children and young adults [5, 6]. To estimate accurately the numbers of deaths attributable to seasonal and to pandemic influenza is difficult, as influenza infections generally are not laboratory confirmed, are not often recognized [7–9] and mostly not specified on hospital discharge forms or death certificates. Additionally many influenza associated deaths occur weeks after the initial infection from secondary complications or from exacerbation of chronic illnesses and in both cases influenza viruses are no longer detectable [10]. The contribution of influenza to these deaths is often not recognized. And even if influenza infection is confirmed by laboratory testing, this rarely leads to influenza as the cause of death on certificates [11]. Furthermore, the influenza virus infection may predispose to other conditions, such as bacterial super infections and cardiovascular complications with the respective diagnoses entered into death certificates. The inability of diagnoses on death certificates to give a reliable and consistent account of the burden of death due to influenza has been understood for many decades and this

understanding led to the development of statistical models to estimate influenza associated deaths. Thus it is standard practice to use statistical modelling techniques to estimate annual deaths associated with influenza [10–14].

For such estimates the complication arises that influenza epidemics often overlap with circulation of other respiratory viruses. In particular with Respiratory Syncytial Virus (RSV) that, like influenza, is associated with excess mortality in all age groups [9, 10, 15]. In order to avoid an overestimation of the impact of influenza on mortality in years with substantial co-circulation of influenza and RSV, models have to be adjusted for the confounding effect of RSV.

Although estimates on the burden of influenza and the incidence of influenza associated deaths based on various models are available for many European countries [16], data comparing seasonal and pandemic influenza mortality using the same statistical methodology have only been published recently for one European country, the Netherlands [17]. Since age specific information on influenza associated mortality in Austria is not available, we decided to estimate and compare the number of influenza attributable deaths in different age groups for ten seasonal and the pandemic wave in Austria applying the same methodology. For this purpose age-specific non-violent cause as well as cause specific mortality was related to influenza virus activity in the Viennese population adjusted for the potential confounding effect of co-circulating RSV using the same Poisson model for all 11 seasons investigated. Carefully performed region specific estimates are important to assess the impact of the 2009/2010 pandemic on the European population.

Materials and methods

Study population

Reported cases of death of inhabitants of the city of Vienna from 1 Jan 1999 through 31 Dec 2009 were provided by Statistik Austria. The file contained gender, age at death, district of the last registered address, day of death, and four digit International Classification of Diseases (ICD) code (9th revision till end of 2001 and 10th revision afterwards). All cases of deaths of citizens of Austria with their residence in Vienna and their place of death in Vienna were included in the analysis. Population size of Vienna was 1.54 million in 1999 and 1.70 million in 2010.

Viral surveillance

National viral influenza surveillance

Laboratory based surveillance for influenza viruses is conducted annually from October through April (calendar week 40 through week 16 of the following year). The virological data are based on the detection of influenza viruses by Polymerase Chain Reaction (PCR) and by virus isolation in nasopharyngeal swabs (NPS) collected from a subset of patients by sentinel physicians (general practitioners and paediatricians throughout Austria) forming part of the Diagnostic Influenza Surveillance Network Austria (DINOE) and sent to the Department of Virology, Medical University Vienna for further analysis. In addition to the sentinel samples, analyses were also performed with viruses detected in NPS sent to the department from hospitals, paediatricians and unaffiliated physicians. Detection, typing and subtyping of influenza viruses was performed as described previously [18].

RSV surveillance

Nasopharyngeal aspirates (NPA) were obtained from children admitted to the St. Anna Children's Hospital, Vienna, with acute respiratory symptoms, including fever, cough, rhinorrhoea, dyspnoea, tachypnoea, rhinitis, bronchiolitis, bronchitis, and pneumonia. The NPA was obtained within 24 h after admission to the hospital by suction from the nasopharynx, using a tracheal suction kit (Nunc, Kampstrup, Denmark) [19]. In addition to these samples, analyses were also performed from NPS sent to the department from hospitals, paediatricians and unaffiliated physicians. RSV-PCR was performed as described previously [20].

Definition of influenza virus epidemic/pandemic activity and periods of increased RSV activity

For the calculation of the influenza attributable deaths by the Poisson model it was mandatory to define the weeks of epidemic/pandemic influenza virus activity. The definition used by the National Respiratory and Enteric Virus Surveillance System and Aberle et al. [19, 21] for increased RSV and human Metapneumovirus activity was therefore adapted for influenza virus: the onset of epidemic/pandemic activity was defined as the first of two consecutive weeks where >10 % of NPA were tested positive by PCR, and the end was defined as the last week in which >10 % were positive, followed by two consecutive weeks of <10 % positive tests.

In order to adjust for the possible confounding effect of RSV on mortality the absolute numbers of RSV positive specimens per each week of the 11 years investigated were included as a co-factor in the Poisson calculation.

To provide graphical information on the co-circulation of RSV and influenza viruses within the influenza surveillance periods (Fig. 1), periods of increased RSV activity were defined according to the criteria of Jansen

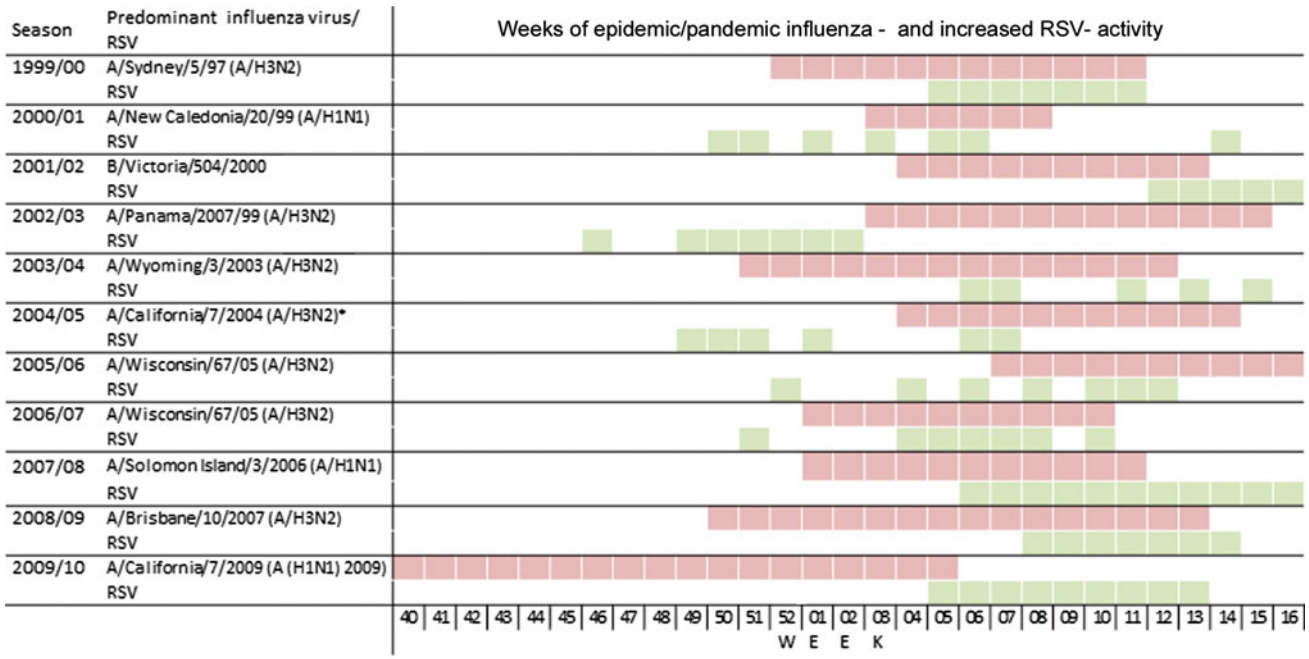

Fig. 1 An overview on the annual epidemic/pandemic influenza and increased RSV activity from seasons 1999/2000 to 2009/2010 from week 40 of 1 year to week 16 of the following year. Onset of Influenza epidemic/pandemic activity was defined as the first of 2 consecutive weeks where >10 % of NPA tested positive by PCR, and end of activity was defined as the last week in which >10 % were positive, preceding 2 consecutive weeks of <10 % positive tests. Increased RSV activity was defined as those weeks in which PCR positive RSV specimens accounted for ≥5 % of the season's total number of laboratory confirmed RSV cases. (Color figure online)

et al. [9] (at least two consecutive weeks in which each week accounted for >5 % of the season's total number of positive tests for RSV). Co-circulation of influenza and RSV was defined as a coincidence of at least 3 weeks of epidemic/pandemic influenza activity and an increased RSV activity.

Statistical analysis

Mortality data were analysed for the period June 1st, 1999 until May 31st, 2010. Over this period baseline mortality was modelled by long-term time trend parameters and parameters for annual variation from sine and cosine terms. To estimate the contribution of influenza to mortality for the Viennese population Poisson models were applied relating the absolute number of daily deaths in Vienna to the week of influenza season. All weeks with influenza virus epidemic/pandemic activity, as defined above, were included in the model as dummy variables [vector w]. Linear [t] and non-linear [t^2] time trends as well as annual variation of deaths [sine and cosine terms] were included in the model and weekends were specified as dummy variables [we]. As dependent variables daily deaths from all non-violent causes (all codes except ICD9: 800-999, ICD10: S/T), from respiratory diseases (ICD9: 460-519, ICD10: J), and from cardiovascular diseases (ICD9: 390-459, ICD10: I) were included.

The model is specified as follows:

$$E(Y) = \alpha \cdot \exp(\beta_0 + \beta_1[t] + \beta_2[t^2] + \beta_3\left[\sin\left(\frac{2\pi t}{d}\right)\right] + \beta_4\left[\cos\left(\frac{2\pi t}{d}\right)\right] + \beta_5[we] + \beta_6[\mathrm{RSV}_t] + \overrightarrow{\gamma}[\overrightarrow{w}])$$

where $E(Y)$ is the expected number of deaths at day t (days after January, 1st 1999) in a year with d days (365 or 366), that is a weekend-day or not ($we = 1$ or 0) and is or is not a day of the 1st to k-th weeks of the influenza season (dummy vector w). Alpha is the offset variable equal to the respective population size. RSV_t is the number of RSV-positive test results on day t. β_0–β_6 and the vector γ are estimated by maximum-likelihood methods using S-Plus 6.2 (Insightful Corp.) procedure gam (general additive model) with family 'poisson'.

The number of deaths attributable to influenza for week j (AD_j) of the influenza season is calculated according to the following formula:

$$AD_j = D_j \cdot (1 - e^{-\gamma_j})$$

where D_j is the observed number of deaths in week j, and γ_j is the hazard parameter for week j, as estimated by the Poisson model.

To obtain a significance test for comparison of deaths between pandemic and seasonal influenza an approximate variance for the number of attributable deaths was calculated by the delta method which leads to the following expression:

$$\sigma^2_{AD_j} = D_j\left[e^{-2\gamma_j}(1 + D_j\sigma^2_{\gamma_j}) + 1 - 2e^{-\gamma_j}\right]$$

The variance of the number of attributable deaths for the whole season is the sum of the variances for all weeks of influenza virus activity. The test statistic for the hypothesis for the equality of attributable deaths is the difference between the annual attributable deaths divided by the standard deviation of this difference. This test statistic has an approximate normal distribution.

Calculation of the number of life-years lost was based on the annual life-tables for Vienna. For seasonal and pandemic (2009/2010) influenza the life tables of the respective years were geometrically averaged and the attributable deaths within the 10-year age ranges multiplied by the further life-expectancy at the mean of these age-ranges. The sum of these figures divided by the number of seasons gives the expected seasonal number of life-years lost.

Results

From March 1, 1999 to May 31, 2010 overall 176,105 non-violent deaths were registered, of which 9,068 were of respiratory and 89,768 were of cardiovascular causes. The age distribution of the non-violent deaths was as follows: 0.7 % (0–14-years of age), 0.3 % (15–24-years), 11.8 % (25–59 years), and 87.2 % (aged ≥60 years).

Annual influenza virus and RSV surveillance

National influenza and RSV surveillance data are summarized in Table 1. Influenza laboratory data are available from November 1999 to April 2010. During the ten seasonal influenza epidemics from 1999/2000 to 2008/2009, a total of 9,592 specimens were tested for influenza virus (Table 1), of which 3,252 specimens (33.9 %) were positive for influenza viruses. An annual mean of 959 specimens (range 288–1,827) were tested for the presence of influenza viruses during each of the influenza surveillance periods, of those a mean of 325 (33.9 %) specimens were tested positive for influenza virus. Influenza B, A(H1N1), A(H3N2) and A/unsubtyped viruses, respectively, comprised 17.5, 13.7, 47.7 and 21.1 % of the positive influenza samples.

During the influenza pandemic season 2009/2010 1,950 (39.4 %) out of 4,947 specimens were tested positive for influenza A(H1N1)2009. No other influenza A subtype and only two (0.04 %) influenza B viruses were detected.

During the RSV surveillance periods from November 1999 to April 2009 3,717 specimens were tested for RSV and 1,065 (28.7 %) of them showed positive results. The annual mean number of specimens tested for RSV was 372 (range 156–1,235) with an average of 107 (28.8 %) specimens positive per season. During the influenza pandemic season 2009/2010, 99 (10.5 %) out of 940 specimens tested were positive for RSV.

An increased RSV activity during this winter season occurred between week 5 and 13/2010, as can be seen in Fig. 1 which illustrates the weeks of annual epidemic/pandemic influenza virus activity and the periods of increased RSV activity during the different seasons investigated. Co-circulation of influenza and RSV, as defined above occurred in seven of the eleven seasons analysed. The total number of weekly nonviolent, respiratory-, and cardiovascular deaths of the Viennese population in relation to the activity of influenza viruses and RSV in the seasons investigated are provided in Fig. 2a–c. As illustrated, peaks of influenza virus activity are consistently associated with peaks of non-violent, respiratory and cardiovascular deaths.

Using our model, adjusted for the confounding effect of RSV, we calculated the total number of influenza attributable deaths in the Viennese population per season for the 10 influenza periods with seasonal influenza virus activity and for the pandemic wave within non-violent, respiratory-, and cardiovascular deaths.

The number of influenza attributable non-violent deaths ranged from 4.4 to 50 per 100,000 per season, for respiratory deaths from 0.9 to 9.8 per 100,000 and for cardiovascular deaths from 2.6 to 30.5 per 100,000. The average number of the ten seasonal epidemics and those of the pandemic period for Vienna are provided in Table 2, the projection to the incidence per 100,000 population is stated in Table 3. In the group of non-violent deaths the estimated average number of influenza attributable deaths in Vienna was 316 deaths per seasonal and 264 for the pandemic influenza period. This reveals a 16 % reduction in the number of deaths during the pandemic influenza A(H1N1)2009 period compared to the average of the ten previous influenza epidemics. A decrease could also be observed in respiratory (65 vs. 57 deaths, minus 12 %) and cardiovascular attributable deaths (191 vs. 159, minus 17 %) during the pandemic.

Comparing the average numbers of influenza associated deaths in the different age groups of seasonal influenza epidemics with those of the pandemic period, significant differences were observed. A statistically significant increase of the number of influenza attributable deaths for the pandemic period compared to the average number of the ten previous influenza seasons could be observed in the age-groups of 0–14 years (3.8 times more influenza associated deaths in the pandemic compared to seasonal influenza waves, $p < 0.001$)

Table 1 National influenza and RSV surveillance data from season 1999/2000 to 2008/2009 and the pandemic season 2009/2010: number of samples tested and number of positive influenza (including influenza types/subtypes) and RSV-positive specimen

	Influenza								RSV	
Season	Specimen tested	Influenza pos (%)[a]	Inf B pos (%)[b]	Inf A pos (%)[b]	A/H1 pos (%)[b]	A/H3 pos (%)[b]	A/H1 (2009) pos (%)[b]	A n.s. (%)[b]	Specimen tested	RSV pos (%)[a]
1999/2000	319	115 (36.1)	0 (0)	115 (100.0)	0 (0)	67 (58.3)	ND	48 (41.7)	238	97 (40.8)
2000/2001	288	122 (42.4)	12 (9.8)	110 (90.2)	66 (54.1)	1 (0.8)	ND	43 (35.2)	180	76 (42.2)
2001/2002	449	205 (45.7)	129 (62.9)	76 (37.1)	0 (0)	76 (37.1)	ND	0 (0)	167	54 (32.3)
2002/2003	874	510 (58.4)	45 (8.8)	465 (91.2)	2 (0.4)	90 (17.6)	ND	373 (73.1)	201	68 (33.8)
2003/2004	843	333 (39.5)	1 (0.3)	332 (99.7)	1 (0.3)	110 (33.0)	ND	221 (66.4)	230	69 (30.0)
2004/2005	1,087	440 (40.5)	171 (38.9)	269 (61.1)	51 (11.6)	218 (49.5)	ND	0 (0)	189	70 (37.0)
2005/2006	859	245 (28.5)	67 (27.3)	178 (72.7)	7 (2.9)	171 (69.8)	ND	0 (0)	251	103 (41.0)
2006/2007	1,827	430 (23.5)	4 (0.9)	426 (99.1)	21 (4.9)	405 (94.2)	ND	0 (0)	156	122 (78.2)
2007/2008	1,533	341 (22.2)	53 (15.5)	288 (84.5)	287 (84.2)	1 (0.3)	ND	0 (0)	1,235	204 (16.5)
2008/2009	1,513	511 (33.8)	88 (17.2)	423 (82.8)	11 (2.2)	412 (80.6)	ND	0 (0)	870	202 (23.2)
2009/2010	4,947	1,952 (39.5)	2 (0.1)	1,950 (99.9)	0 (0)	0 (0)	1,950 (99.9)	0 (0)	940	99 (10.5)

ND not done

n.s. not subtyped

[a] Percentage of influenza/RSV positive specimen

[b] Percentage of influenza types, subtypes and of not subtyped specimens

and in those 15–24 years of age (2.3 times more pandemic influenza associated deaths; $p < 0.001$). These results are additionally illustrated in Fig. 3, which provides more detailed age-related information on the average number of influenza attributable deaths during seasonal epidemics and the pandemic period. As expected a sharp increase in the number of deaths attributable to influenza was observed for all influenza periods in the elderly (older than 65 years of age), but the results for the pandemic influenza season 2009/2010 demonstrated a less pronounced increase of influenza associated deaths in this age group. Frequencies of attributable deaths for the age group 55–64 years and for all older age groups were significantly lower ($p < 0.001$) in the pandemic season compared to the previous 10 seasons.

Analysis of the number of deaths associated with influenza in the different seasonal epidemics, revealed substantial variation. Influenza attributable deaths of the seasons 2000/2001, 2001/2002, 2005/2006, 2006/2007 and 2007/2008 ranged from 4.4 to 13.9 per 100,000 and were therefore lower than that observed during the pandemic period (15.6 per 100,000). A higher overall mortality compared to the pandemic wave was observed for the influenza seasons of the years 1999/2000, 2002/2003, 2003/2004, 2004/2005, and 2008/2009 ranging from 18.3 to 50 attributable deaths per 100,000. Although there were this substantial differences in the number of influenza attributable deaths between the ten seasonal epidemics, the contribution of the different age groups to the overall number of attributable deaths was consistent with an increase in the number of deaths in the older age groups (≥60 years). In contrast to the seasonal epidemics, the highest number of influenza associated deaths in the lower age groups (0–14 and 15–24 years) was observed during the pandemic season. In those 0–14 years of age pandemic influenza associated mortality was 4.6 per 100,000 compared to a range of 0–2.1 per 100,000 during the seasonal epidemics. In adolescents and young adults between 15 and 24 years pandemic mortality was 3.5 per 100,000 compared to a range of 0–2.7 per 100,000 during the seasonal epidemics.

The calculation on the number of life years lost for the Viennese population revealed an average of 3,830 life years lost (238 years per 100,000 inhabitants) for seasonal influenza epidemics and 4,370 (257 years per 100,000 inhabitants) for the pandemic influenza period, showing no statistically significant difference between the pandemic period and the ten previous seasonal influenza epidemics.

Discussion

It has long been recognized, that influenza is associated with substantial mortality during both, pandemics and epidemics. Different models have been applied in the past

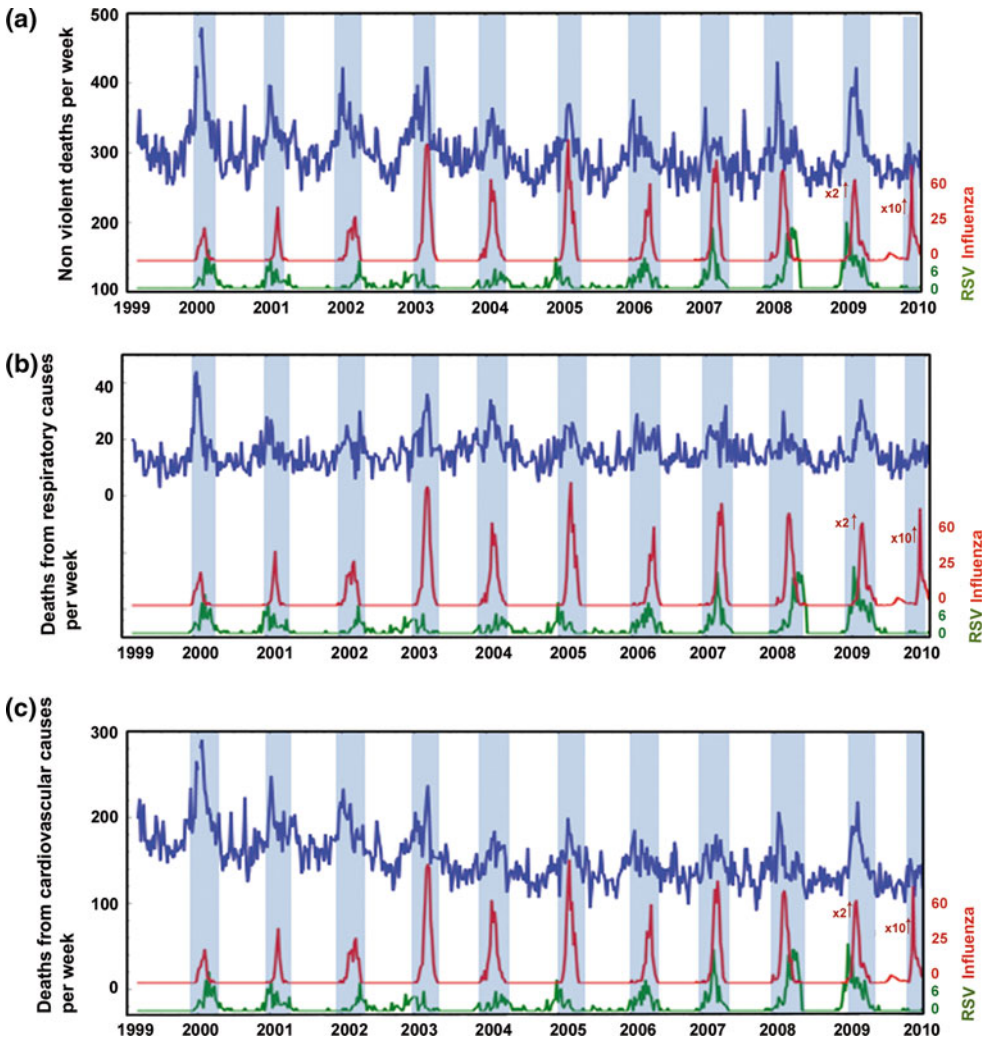

Fig. 2 The total number of nonviolent (**a**), respiratory- (**b**), and cardiovascular (**c**) deaths per week in Vienna in relation to the activity of influenza viruses and RSV in the seasons investigated; *blue line* number of deaths per week, *red line* number of detected influenza viruses per week, *green line* number of RSV detections per week, *light blue areas* time period of influenza virus activity. (Color figure online)

Table 2 Influenza virus attributable death (AD) in the Viennese population per season for 1999/2000–2008/2009 and for the season 2009/2010 for non violent causes (all ICD10 codes except S and T), respiratory diseases (ICD10: J), and cardiovascular diseases (ICD10: I)

Age group	Non violent causes		Respiratory diseases		Cardiovascular diseases	
	1999/2000–2008/2009	2009/2010	1999/2000–2008/2009	2009/2010	1999/2000–2008/2009	2009/2010
Total	316	264	65	57	191	159
0–14	3	11	1	3	2	0
15–24	3	7	0	1	0	2
25–59	35	47	6	12	13	17
≥60	275	199	58	41	176	140

to estimate the impact of influenza on mortality: cyclical regression [12, 13], multivariate linear regression [22, 23], and autoregressive integrated moving average models [14]. Poisson models similar to that applied in this study were successfully applied previously [10, 24, 25]. The advantages of the Poisson model are the possibility to incorporate terms for seasonal variation and time trends of mortality, the flexibility of adding additional explanatory variables if necessary, as RSV activity in our case, and the nature of the distribution of daily (or weekly) deaths.

Based on Poisson modelling using weekly influenza and RSV surveillance data and daily mortality data, we have estimated the impact of influenza adjusted for RSV circulation for the Viennese population in ten seasons prior to and during the pandemic influenza A(H1N1)2009 period. The projection of the Viennese results for the total Austrian

Table 3 Incidence per 100,000 of influenza virus attributable death (AD) in the Viennese population per season for 1999/2000–2008/2009 and for the season 2009/2010 for non violent causes (all ICD10 codes except S and T), respiratory diseases (ICD10: J), and cardiovascular diseases (ICD10: I)

Age group	Non violent causes		Respiratory diseases		Cardiovascular diseases	
	1999/2000–2008/2009	2009/2010	1999/2000–2008/2009	2009/2010	1999/2000–2008/2009	2009/2010
Total	19.1	15.6	3.9	3.4	11.5	9.4
0–14	1.2	4.6	0.4	1.2	0.6	0.0
15–24	1.5	3.5	0.2	0.5	0.0	1.0
25–59	4.1	5.4	0.7	1.4	1.5	2.0
≥60	75.6	52.2	16.0	10.8	48.4	36.7

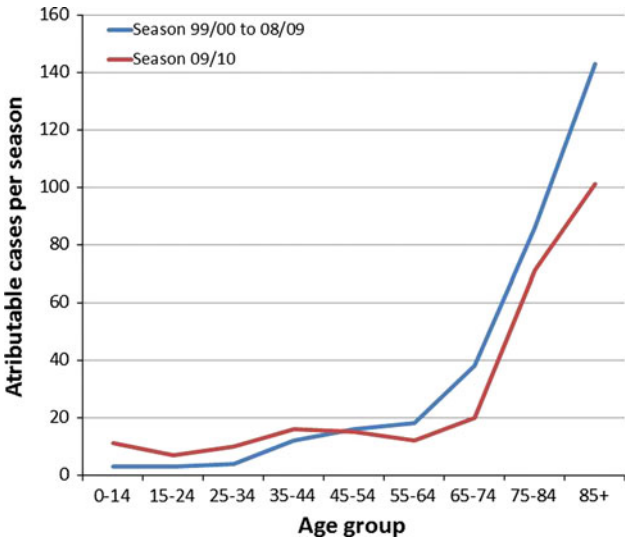

Fig. 3 The comparison of seasonal and pandemic influenza attributable deaths in Vienna by *age-groups*

population reveals an average of about 1,300 deaths for seasonal influenza epidemics (range 360–4000), and of about 1,000 for the pandemic period. The average of influenza-associated excess mortality for seasonal influenza viruses of 19.1 per 100,000 population that we obtained for Vienna (and 15.5 per 100,000 for Austria) is plausible and comparable to previously published data from other developed countries. Researchers in Germany, the Netherlands, the USA and Switzerland estimated for their countries an influenza-related annual mortality of 16, 14, 19.6 and 21.6 per 100,000 population [10, 16, 24, 26], respectively showing, that our findings are well within the range of these results. In our study the comparison of influenza attributable mortality from seasonal influenza with that during the pandemic season 2009/2010 showed, that pandemic influenza A(H1N1)2009 virus was not associated with an increase in non-violent deaths compared to the average of the previous influenza seasons, rather a decrease for the total number could be observed. Analysing influenza associated mortality of the ten individual seasonal epidemics revealed a substantial variation in the numbers of deaths with a higher mortality in five influenza epidemics compared to the pandemic season. Each of this five seasons was dominated by Influenza A(H3N2) viruses and in two of them (2003/2004 and 2004/2005) a significant drift of the dominating influenza viruses had occurred (season 2003/2004: drift from A/Panama/2007/1999 to A/Wyoming/3/2003 and season 2004/2005: drift from A/Wyoming/3/2003 to A/California/7/2004). In contrast, the seasonal epidemics showing a lower mortality compared to the pandemic, were either dominated by Influenza A(H1N1) or B viruses (seasons 2000/2001, 2001/2002 and 2007/2008), or were dominated by A(H3N2) viruses in their fourth or fifth year of consecutive dominant circulation (seasons 2005/2006 and 2006/2007), most probably leading to a broad cross reactive immunity in the population and therefore to a reduced morbidity and mortality. However, the remarkable feature of the pandemic season was, that the highest number of attributable deaths of all the seasons investigated was observed in children and young adults. This special feature of the pandemic season was also observed for The Netherlands [17], with a particularly high incidence in those 0–4 years of age (8.3 attributable cases per 100,000). In this study influenza like illness (ILI) was used to define periods of influenza activity in the Dutch population. ILI can be caused by a variety of different respiratory pathogens and severe disease due to these pathogens is most commonly observed in infants. Choosing this way to model the association of mortality with influenza activity may result in an overestimation of influenza associated deaths in the very young. The influenza mortality in our youngest age group (0–14 years) was 4.6 per 100,000. Due to the low number of deaths in this young age group in Vienna (see Tables 2, 3), no further break down into subgroups was possible. However, the overall trend (Fig. 3) suggests that also in Vienna the burden of deaths could have been highest in those below 5 years of age.

An increased mortality in younger age groups for pandemic influenza A(H1N1)2009 compared to seasonal influenza epidemics has also been reported in various studies

conducted worldwide [4, 5, 27–35]. These differences are most probably due to the fact that adults and elderly, particularly those born before 1957 and likely exposed to previous influenza viruses antigenically related to the recent A(H1N1)2009 virus, seem to be more protected [36, 37] than younger people. This is also reflected by the reports of a more severe course of influenza A(H1N1)2009 infection in children and young adults [37, 38].

Although our data show a decrease in the total number of influenza associated deaths during the pandemic 2009/2010, the total number of life years lost is not significantly different between seasonal epidemics and the pandemic influenza period due to the higher number of deaths at younger age during the pandemic period.

In our study on estimating age specific influenza mortality, the confounding effect of RSV was taken into consideration by including the absolute number of RSV positive specimens as a parameter in our model. The possible bias of an increased number of RSV positive specimens due to enhanced testing during the pandemic influenza period can be excluded since enhanced testing for RSV was not observed during the 2009/2010 season (Table 1). Besides that, activities of influenza and RSV were not overlapping in the 2009/2010 season (Fig. 1).

However, RSV is not the only possible confounder: different other respiratory pathogens, climate factors, air pollution and other variables that exhibit seasonal variation could also confound the relationship between influenza activity and time series of deaths. Seasonal temperature trends are at least partly accounted for in the model by the wave terms, but higher order oscillations are not considered. Air pollution demonstrates also seasonal patterns with high levels of some of these pollutants (e.g. particulate matter) during the winter season with a more or less pronounced overlap with influenza activity. Some preliminary analyses using time series of climate and air pollution data showed only very low correlation with influenza and RSV activity when restricting analysis to the winter season. This indicates that effects on estimates of attributable deaths are possibly small. However, this issue needs further study and should be addressed in future investigations.

In summary, the strength of our study was, that we were able to compare pandemic to seasonal influenza associated deaths in different age groups by using the same statistical methods and data types derived from the same urban population for both pandemic and seasonal influenza periods.

Using the Poisson model including viral data of the influenza and RSV surveillance system, and deaths reports over eleven consecutive influenza periods, extending to the pandemic wave 2009/2010, provided reliable age specific estimates of influenza mortality for Vienna and provide a basis for a rough estimate of influenza associated deaths in Austria. Therefore our data contribute to the completion of the general view on the mortality burden of seasonal and pandemic influenza in Europe.

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