All-cause versus cause-specific excess mortality for the estimation of influenza-associated mortality in Denmark, Spain, and the United States

Sebastian S S Schmidt [1 *], A Danielle Iuliano, PhD [2], Lasse S Vestergaard, PhD [1], Clara Mazagatos-Ateca [3], Amparo Larrauri, PhD [3], Jan M Brauner [4], Sonja J Olsen, PhD [5], Jens Nielsen, PhD [1], Joshua A Salomon, PhD [6], Tyra G Krause, PhD [1]

[1)] Statens Serum Institut, Copenhagen, Denmark
[2)] Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA
[3)] National Centre of Epidemiology, CIBER Epidemiología y Salud Pública (CIBERESP), Carlos III Health Institute, Madrid, Spain
[4)] Department of Computer Science, University of Oxford, Oxford, United Kingdom
[5)] World Health Organization Regional Office for Europe, Copenhagen, Denmark
[6)] Department of Medicine, Stanford University, Palo Alto, CA, USA

Background: Excess mortality due to seasonal influenza is substantial, and pandemics like COVID-19 call for timely mortality estimates. Methods used to estimate influenza-associated mortality typically use all-cause deaths, which is readily available in many countries, or cause-specific mortality data, which may be more specific to influenza but have substantial delays.

Method: For Denmark, Spain, and the United States, we estimated age-stratified excess mortality for i) all-cause, ii) pneumonia and influenza, iii) respiratory and circulatory, iv) respiratory, and v) circulatory causes of death for the 2015/16 and 2016/17 seasons. We quantified differences between the different categories with respect to their weekly and seasonal excess mortality estimates. The estimates were obtained using the EuroMOMO model on mortality data from 2010 through 2017.

Results: The respective periods of weekly excess mortality for all-cause and cause-specific deaths were similar in their chronological patterns. Seasonal all-cause excess mortality estimates for the 2015/16 and 2016/17 seasons were 15,068 deaths (10,582-19,558) and 46,292 deaths (42,047-50,540), for the United States. For Denmark they were 20.3 (15.8-25.0) and 24.0 (19.3-28.7) per 100,000 population. For Spain they were 22.9 (18.9-26.9) and 52.9 (49.1-56.8) per 100,000 population. Seasonal respiratory and circulatory excess mortality estimates were two to three times lower than the all-cause estimates.

Discussion: There are benefits to using a simple model based on all-cause mortality as it is timely and may approximate cause-specific estimates and the influenza-associated mortality. These findings have important implications for the development of future timely mortality monitoring systems during pandemics such as COVID-19.

Word count: 248 (abstract) / 3444 (main text).

Keywords

Excess Mortality; Influenza; Influenza-associated mortality; Monitoring; Time-series analysis; EuroMOMO.

*) Corresponding author: Disease Epidemiology and Prevention, Statens Serum Institut, Copenhagen S, Denmark. Email: sssu@ssi.dk ; sebastians.s.s@live.dk

1. Introduction

Globally, influenza has been estimated to be associated with up to 646,000 respiratory deaths annually with significant seasonal variation (1). Furthermore, periodic influenza pandemics can result in much greater mortality. The 1918 influenza pandemic resulted in approximately 50 million deaths and reduced the life-expectancy in the United States by 12 years (2). However, the risks posed by new strains of respiratory viruses have never been more salient (3). This indicates a need for robust and timely mortality estimates for assessing risks and prioritizing public health interventions during seasonal influenza epidemics and during novel virus pandemics.

There are many different methods used for estimating the influenza-associated mortality (1,4–7). One important distinguishing factor is whether they use all-cause or select cause-specific mortality data.

All-cause mortality data are, by definition, multi-causal, and it is only possible to associate excess mortality to underlying causes (e.g., influenza) by assessing the correlation over time with specific indicators. Because of this multi-causality, all-cause excess mortality may overestimate the true number of deaths associated with one cause (8). However, during winter seasons in temperate zones, increases in all-cause mortality are often observed, and the circulation of influenza has been shown to be the main seasonal driver of this excess mortality, although other factors (such as extreme temperatures and other respiratory viruses) may contribute as well (8–10). Furthermore, all-cause mortality data are readily available in many countries with short delay and can be used for weekly monitoring to inform timely risk assessments of a wide range of threats (11).

Cause-specific mortality data, on the other hand, can be more disease-specific and may provide estimates that are more accurate. However, the categories commonly used for estimating the influenza-associated mortality (such as respiratory diseases) are also multi-causal and contain many causes unrelated to events of interest for monitoring of influenza-associated mortality (1). Due to the higher specificity, models based on cause-specific data (e.g., respiratory diseases) tend to lose sensitivity and may underestimate the total number of deaths associated with influenza (1,8,12–14). Furthermore, processes to code, clean, and validate the data are currently causing up to two years of delays in most countries. For these reasons, cause-specific mortality data may be less suitable and less timely for real-time monitoring purposes.

The true influenza burden is likely to be between these two data sources used in estimation. Therefore, cause-specific mortality data are valuable for validating excess mortality estimates derived from all-cause mortality data. However, few direct comparisons between the estimates obtained using these two data sources have been made.

Emerging threats like the COVID-19 pandemic highlight the utility of monitoring all-cause mortality in real-time. By the time global guidance for coding deaths due to COVID-19 was released on 16 April 2020, 131,034 global deaths were already reported (3,15). However, it has become apparent through estimates of all-cause excess mortality that the reporting is likely a gross underestimate (16,17).

Since 2009, the European network for monitoring of excess mortality for public health action, EuroMOMO, has monitored weekly all-cause mortality in up to 24 participating European countries and provided pooled estimates of excess mortality (observed deaths minus baseline deaths), using the EuroMOMO model (11,18–20).

We examined the differences between using all-cause and select cause-specific mortality data for estimating mortality related to influenza. We did this by applying the EuroMOMO model to i) all-cause, ii) pneumonia and influenza (P&I), iii) respiratory and circulatory, iv) respiratory, and v) circulatory mortality data. We compared the weekly and seasonal cumulative excess mortality estimates using data from Denmark, Spain, and the United States for the 2015/16 and 2016/17 seasons and compared these estimates with official estimates from the national public health authorities in these countries.

2. Material and Methods

2.1 Data sources

2.1.1 Mortality data

To estimate the weekly mortality attributable to influenza, we used mortality data by age group (0 to 64, 65 to 74, and ≥75 years) from the 2010/11 through the 2016/17 season. Deaths were categorized using the International Classification of Diseases, 10th Revision (ICD-10) codes. We focused on underlying causes of death categorized as all-cause (A00-Y99), diseases of the circulatory system (I00-I99), diseases of the respiratory system (J00-J99), influenza (J9-J11), and pneumonia (J12-J18). For each mortality record, the primary underlying cause was listed, defined as “the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.” as specified by ICD-10 (21).

For Denmark, the mortality data were obtained as individual notifications with the underlying cause of death, dates of deaths, and dates of birth from the Danish Civil Registry. For the United States, the mortality data were obtained as weekly aggregated age group-specific data from the National Center for Health Statistics (NCHS). For Spain, the mortality data were obtained as weekly aggregated age group-specific data from computerized civil registers covering 92% of the total Spanish population through the Centro Nacional de Epidemiología, Instituto de Salud Carlos III (CNE-ISCIII).

2.1.2 Mortality rates - population data

Based on the estimated number of deaths, mortality rates were calculated using national population data as of January 1st every year and linearly interpolated through the year. For Denmark and Spain, the population data was downloaded from Eurostat in week 5/2020 (22). For the United States, the population data were obtained from the United States Census Bureau (23).

2.2 The EuroMOMO model

The model is a time-series regression model using a Poisson distribution and corrected for overdispersion and ISO-week[1] as the time unit, and the number of weekly deaths as the dependent variable adjusting for time trends and seasonal variation (18). Some of the main outputs are: total weekly number of deaths corrected for delay in registration, expected weekly number of deaths (baseline), weekly number of excess deaths (defined as observed number minus the expected number of deaths) and standard deviation around the baseline (z-score) by all ages and stratified into age groups. The baseline was estimated based on the five preceding seasons

[1] ISO-weeks is a widely leap week calendar system where each year has either 52 or 53 full weeks. It was issued by the International Organization for Standardization and has been adopted by the European Committee for Standardization.

(2010/11 through 2014/15) during the period of the year when it was assumed that additional factors that can lead to excess deaths are not likely to happen (primarily influenza and heat waves). These periods are relatively short compared to the whole of the series and are defined as “Spring” from week 15 to week 26 and “Autumn” from week 36 to week 45.

2.3 Analysis

2.3.1 Arriving at the excess mortality estimates

The baseline for weekly mortality for season 2015/16 and 2016/17 was estimated by fitting the EuroMOMO model to the mortality data for the five preceding seasons. The weekly excess mortality estimates were calculated by subtracting the baseline mortality from the observed mortality.

2.3.2 Weekly all-cause excess mortality compared to excess cause-specific

To evaluate differences in the weekly excess mortality estimates for all ages, we plotted the observed mortality rates and the baseline mortality rates for each cause of death and visually compared the respective excess mortality periods. All estimates were converted to mortality rates per 100,000 population and adjusted for age according to the WHO World Standard Population (24).

2.3.3 Seasonal all-cause excess mortality compared to excess cause-specific

To evaluate differences by season, we summed the weekly excess mortality estimates - without truncating negative excess estimates - within the entire period where the influenza season can possibly occur (week 40 of one year through week 20 of the following year) for season 2015/16 and 2016/17. We compared these estimates with the influenza-associated mortality estimates published by the national public health authorities in Denmark, Spain, and the United States.

3. Results

Weekly all-cause and cause-specific excess mortality - The United States

Within the possible influenza season (week 40 to week 20), there were distinct periods with excess mortality for all-cause and cause-specific mortality (Figure 1). For each year, the period of excess mortality for all-cause and the cause-specific mortality were similar to each other in terms of when the excess mortality started, the timing of peaks, and the length of the period. The 2015/16 season had little excess mortality across all-cause and cause-specific mortality, and the period with excess mortality started later compared to the 2016/17 season.

Weekly all-cause and cause-specific excess mortality – Spain

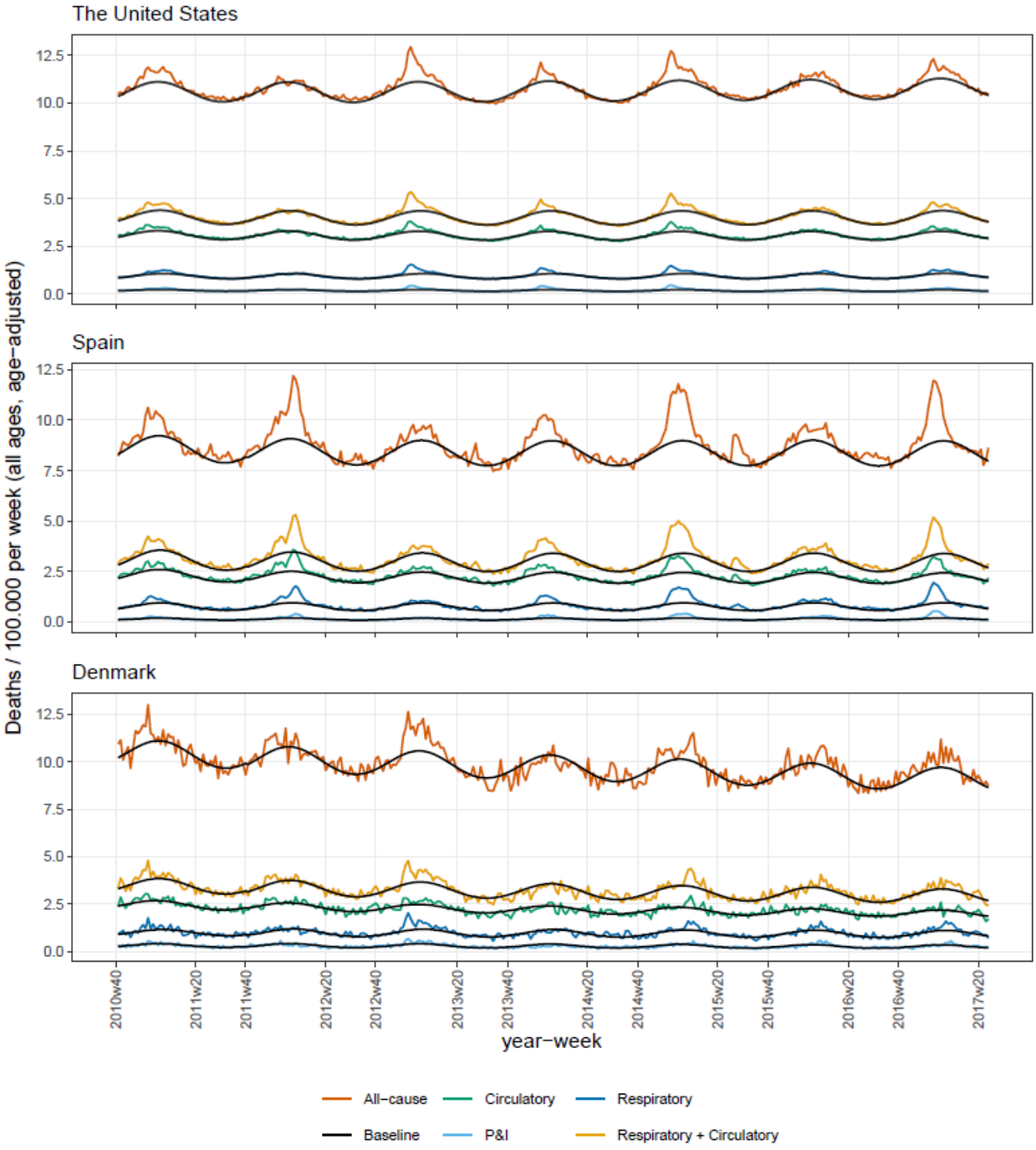
Within the possible influenza season, there were distinct periods with excess mortality for all-cause and cause-specific mortality (Figure 1). The periods with excess mortality for circulatory mortality were similar to all-cause mortality with respect to when the excess mortality started, the timing of peaks, and the length of the period. The periods with excess mortality for P&I and respiratory mortality tended to start later than all-cause and circulatory mortality, but the peaks were synchronous. There was significantly more excess mortality in the 2016/17 season than in the 2015/16 season.

Weekly all-cause and cause-specific excess mortality – Denmark

Within the possible influenza season, we observed periods with excess mortality across all-cause and cause-specific mortality (Figure 1). However, it was more difficult to determine the periods of excess mortality

due to the smaller population size. In particular, we observed distinct periods of excess mortality in respiratory and all-cause mortality. Compared to all-cause excess mortality, the respiratory and P&I excess mortality started later, were shorter in length but similar in the timing of peaks.

Figure 1: Weekly age-adjusted mortality per 100.000 population for all-cause, respiratory and circulatory, circulatory, respiratory, and pneumonia and influenza, week 40/2010 to week 20/2017, in the United States, Spain, and Denmark.



The modeled baseline is based on the EuroMOMO model. Excess mortality is defined as the observed mortality minus the baseline mortality. Note that anything before week 40 of 2015 has been used to estimate the baseline, and therefore the excess mortality will not be examined for that period.

Seasonal all-cause and cause-specific excess mortality – The United States

For all ages, the mean excess mortality for the two seasons based on all-cause, respiratory and circulatory, circulatory, respiratory, and P&I was 9.50, 4.30, 2.20, 2.09, and 1.01 per 100.000 population, respectively (Table 1). These estimates corresponded to 30680, 12429, 7094, 8182, and 3253 deaths, respectively. The excess mortality estimates for the 2016/17 season were around three times as high as those for the 2015/16 season. Influenza A (H1N1)pdm09 viruses predominated during the 2015/16 season, whereas influenza A(H3N2) predominated during the 2016/17 season (Table 1). The ratios between all-cause excess mortality and the excess mortality of the respective cause-specific causes of death all increased from the 2015/16 to the 2016/17 season (Table 2). However, the ratio for P&I excess mortality remained relatively constant for all ages. When stratified by age groups, the ratios remained constant for the age group 0-64, but this was not the case for the other age groups.

Seasonal all-cause and cause-specific excess mortality – Spain

For all ages, the mean excess mortality for the two seasons based on all-cause, respiratory and circulatory, circulatory, respiratory, and P&I was 37.9, 19.6, 9.2, 10.1, and 3.3 per 100.000 population, respectively (Table 1). These mean estimates corresponded to 16197, 8347, 3935, 4300, and 1414 deaths, respectively. The excess estimates for the 2016/17 season were higher than those for the 2015/16 season. Influenza A (H1N1)pdm09 viruses predominated during the 2015/16 season, whereas influenza A(H3N2) predominated during the 2016/17 season (Table 1). The ratios between all-cause excess mortality and the excess mortality of the respective cause-specific causes of death all increased from the 2015/16 to the 2016/17 season (Table 2). However, the ratio for circulatory remained constant for all ages. When stratified by age groups, the ratios were not constant across the two seasons.

Seasonal all-cause and cause-specific excess mortality – Denmark

For all ages, the mean excess mortality during the 2015/16 and 2016/17 seasons based on all-cause, respiratory and circulatory, circulatory, respiratory, and P&I was 22.16, 10.84, 5.12, 5.5, and 1.3 per 100.000 population, respectively (Table 1). These mean estimates corresponded to 1261, 617, 291, 314, and 64 deaths, respectively. The excess mortality estimates were similar across the two seasons except for P&I excess mortality, which decreased by a factor of two in 2016/17. Influenza A (H1N1)pdm09 viruses predominated during the 2015/16 season, whereas influenza A(H3N2) predominated during the 2016/17 season (Table 1). The ratios between all-cause excess mortality and respiratory and circulatory, circulatory, and respiratory excess mortality remained relatively constant across the two seasons but not for P&I excess mortality (Table 2). When stratified by age groups, the ratios between the all-cause excess mortality estimates and the respective cause-specific excess mortality estimates were not constant.

Table 1: Cumulated all-cause, respiratory and circulatory, circulatory, respiratory, and pneumonia and influenza excess mortality during the winter season (week 40 to week 20), based on the EuroMOMO model, for season 2015/16 and 2016/17, in the United States, Spain, and Denmark.

THE UNITED STATES							
Season	**Cause of death**	**All-cause**	**Respiratory + Circulatory**	**Circulatory**	**Respiratory**	**Pneumonia and Influenza**	**Circulating types of influenza[1]**
	Age groups	**Excess mortality per 100.000 population (95%-CI);**					
2015/16	0-64	5.2 (4.7; 5.8)	1.9 (1.7; 2.1)	1.4 (1.2; 1.6)	0.4 (0.3; 0.5)	0.2 (0.2; 0.3)	A(H1N1)pdm09 (57%) A(H3N2) (14%) B/Victoria (29%)
	65-74	5.5 (2.5; 8.5)	5.4 (3.6; 7.2)	4.0 (2.6; 5.4)	1.5 (0.5; 2.5)	1.1 (0.7; 1.5)	
	≥75	-7.6 (-22.2; 7.1)	-6.9 (-15.9; 2.2)	-11.1 (-17.6; -4.5)	4.5 (1.0; 8.1)	2.4 (1.2; 3.7)	
	All ages	4.7 (3.3; 6.1)	1.7 (0.9; 2.4)	0.9 (0.3; 1.4)	0.8 (0.5; 1.1)	0.5 (0.4; 0.6)	
2016/17	**Age groups**	**Excess mortality per 100.000 population (95%-CI);**					___
	0-64	4.9 (4.3; 5.4)	1.6 (1.4; 1.8)	1.3 (1.1; 1.4)	0.3 (0.2; 0.4)	-0.0 (-0.1; 0.0)	A(H3N2) (76%) A(H1N1)pdm09 (2%) B/Yamagata (22%)
	65-74	19.9 (16.9; 22.9)	11.0 (9.4; 12.6)	6.1 (4.7; 7,5)	4.9 (4.0; 5.9)	1.8 (1.5; 2.2)	
	≥75	128.8 (114.8; 143.0)	70.7 (62.6; 78.8)	28.6 (22.5; 34.6)	42.2 (39.1; 45.4)	21.5 (20.2;22.9)	
	All ages	14.3 (13.0; 15.6)	6.9 (6.2; 7.6)	3.5 (3.0; 4.0)	3.4 (3.1; 3.6)	1.6 (1.4; 1.7)	
SPAIN							
Season	**Cause of death**	**All-cause**	**Respiratory + Circulatory**	**Circulatory**	**Respiratory**	**Pneumonia and Influenza**	**Circulating types of influenza[2]**
	Age groups	**Excess mortality per 100.000 population (95%-CI);**					
2015/16	0-64	5.4 (4.8; 6.1)	3.2 (2.9; 3.5)	1.6 (1.3; 1.9)	1.6 (1.4; 1.7)	0.9 (0.8; 1.0)	A(H1N1)pdm09 (61%) Other A (5%) B/Victoria (34%)
	65-74	33.3 (26.0; 40.6)	12.2 (8.2; 16.2)	7.3 (4.0; 10.6)	4.9 (3.2; 6.7)	3.3 (2.6; 4.0)	
	≥75	160.8 (122.9; 199.0)	64.3 (42.1; 86.8)	32.0 (17.2; 47.1)	29.9 (20.0; 39.9)	2.8 (0.2; 5.4)	
	All ages	22.9 (18.9; 26.9)	9.8 (7.5; 12.1)	5.0 (3.5; 6.6)	4.6 (3.6; 5.5)	1.3 (1.0; 1.6)	
2016/17	**Age groups**	**Excess mortality per 100.000 population (95%-CI);**					___
	0-64	4.8 (4.1; 5.5)	2.0 (1.7; 2.3)	1.1 (0.8; 1.4)	0.9 (0.7; 1.0)	0.4 (0.3; 0.5)	A(H3N2) (94%) A(not subtyped) (5%)
	65-74	43.7 (36.6; 50.8)	23.7 (19.8; 27.6)	11.1 (7.8; 14.5)	12.7 (10.9; 14.4)	5.0 (4.3; 5.7)	
	≥75	473.7 (437.0; 510.0)	269.2 (247.8; 290.4)	121.1 (107.0; 135.1)	145.1 (135.2; 155.0)	47.4 (44.5; 50.3)	
	All ages	52.9 (45.2; 52.2)	29.3 (24.9; 28.9)	13.4 (11.0; 13.7)	15.6 (13.4; 15.2)	5.3 (4.6; 5.1)	
DENMARK							
Season	**Cause of death**	**All-cause**	**Respiratory + Circulatory**	**Circulatory**	**Respiratory**	**Pneumonia and Influenza**	**Circulating types of influenza[3]**
	Age groups	**Excess mortality per 100.000 population (95%-CI);**					
2015/16	0-64	8.9 (6.7; 11.2)	2.6 (1.7; 3.5)	0.1 (-0.6; 0.9)	2.4 (2.0; 2.9)	0.6 (0.3; 0.9)	A(H1N1)pdm09 (51%) A(H3N2) (5%) B/Victoria (44%)
	65-74	-17.5 (-34.5; -0.3)	11.4 (2.2; 20.6)	5.2 (-2.4; 12.8)	6.2 (0.8; 11.7)	0.4 (-1.7; 2.6)	
	≥75	191.1 (140.1; 243.0)	78.8 (47.3; 110.9)	54.6 (29.8; 79.7)	22.2 (6.4; 38.3)	13.7 (4.3; 23.4)	
	All ages	20.3 (15.8; 25.0)	9.4 (6.4; 12.3)	4.8 (2.5; 7.1)	4.4 (2.9; 6.0)	1.6 (0.8; 2.3)	
2016/17	**Age groups**	**Excess mortality per 100.000 population (95%-CI);**					___
	0-64	4.2 (2.1; 6.3)	-0.4 (-1.3; 0.5)	-1.1 (-1.9; -0.3)	0.8 (0.3; 1.2)	-0.3 (-0.5; -0.1)	A(H3N2) (97%) A(H1N1)pdm09 (1%) Mixed B (2%)
	65-74	17.5 (1.5; 33.6)	10.3 (1.1; 19.5)	-0.3 (-7.6; 7.1)	10.2 (4.8; 15.6)	1.5 (-0.9; 3.9)	
	≥75	237.1 (185.3; 289.6)	149.2 (116.7; 182.1)	82.4 (57.4; 107.5)	62.7 (46.3; 79.5)	9.5 (0.3; 19.1)	
	All ages	24.0 (19.3; 28.7)	12.3 (9.3; 15.4)	5.4 (3.1; 7.7)	6.6 (5.0; 8.2)	0.7 (-0.1; 1.5)	

Note: The preceding seasons have not been included as they were used for generating the baseline estimates. Furthermore, the columns for each age group do not add up to the all-cause excess, this is to be expected, as they are separate models with separate baselines.[1)] Morbidity and Mortality Weekly Reports (25,26). [2)] Centro Nacional de Epidemiología, Instituto de Salud Carlos III (27,28). [3)] Statens Serums Institut report (29,30)

Table 2: Ratio between cumulated all-cause excess mortality and cumulated respiratory and circulatory, circulatory, respiratory, and pneumonia and influenza excess mortality during the winter season (week 40 to week 20), based on the EuroMOMO model, for season 2015/16 and 2016/17, in the United States, Spain, and Denmark.

THE UNITED STATES						
Season	**Cause of death**	**All-cause**	**Respiratory + Circulatory**	**Circulatory**	**Respiratory**	**Pneumonia and Influenza**
	Age groups					
2015/16	0-64	1.0	0.36	0.27	0.08	0.04
	65-74	1.0	0.99	0.73	0.27	0.20
	≥75	1.0	0.90	1.45	-0.59	-0.32
	All ages	1.0	0.36	0.19	0.17	0.10
	Age groups					
2016/17	0-64	1.0	0.33	0.26	0.06	0.00
	65-74	1.0	0.55	0.31	0.25	0.09
	≥75	1.0	0.55	0.22	0.33	0.17
	All ages	1.0	0.48	0.24	0.24	0.11
SPAIN						
Season	**Cause of death**	**All-cause**	**Respiratory + Circulatory**	**Circulatory**	**Respiratory**	**Pneumonia and Influenza**
	Age groups					
2015/16	0-64	1.0	0.59	0.30	0.30	0.17
	65-74	1.0	0.37	0.22	0.15	0.10
	≥75	1.0	0.40	0.20	0.19	0.02
	All ages	1.0	0.43	0.22	0.20	0.06
	Age groups					
2016/17	0-64	1.0	0.42	0.23	0.19	0.08
	65-74	1.0	0.54	0.25	0.29	0.11
	≥75	1.0	0.57	0.26	0.31	0.10
	All ages	1.0	0.55	0.25	0.29	0.10
DENMARK						
Season	**Cause of death**	**All-cause**	**Respiratory + Circulatory**	**Circulatory**	**Respiratory**	**Pneumonia and Influenza**
	Age groups					
	0-64	1.0	0.29	0.01	0.27	0.06
2015/16	65-74	1.0	-0.65	-0.30	-0.35	-0.02
	≥75	1.0	0.41	0.29	0.12	0.07
	All ages	1.0	0.46	0.24	0.22	0.08
2016/17	**Age groups**					
	0-64	1.0	-0.09	-0.26	0.18	-0.07
	65-74	1.0	0.59	-0.02	0.58	0.08
	≥75	1.0	0.63	0.35	0.26	0.04
	All ages	1.0	0.51	0.23	0.27	0.03

Note: The ratios are based on the corresponding excess mortality estimates in Table 1.

4. Discussion

We found that the periods of weekly excess mortality for all-cause and the respective cause-specific causes of death were generally similar with respect to when the excess periods started, their length, and their timing of peaks, especially for the United States and Spain. Furthermore, we found that these periods were within the period where the influenza season typically occurs (week 40 to week 20 the following year).

The ratios between cumulative seasonal all-cause excess mortality and excess mortality of the cause-specific causes of death (except for P&I) remained constant for Denmark across the two seasons. However, for the

United States, a constant ratio was only observed for P&I mortality, while for Spain, the constant ratio was only observed for circulatory excess mortality. These ratios did not remain constant when stratified by age groups. Overall, this suggests that excess mortality estimates based on all-cause may be used to infer excess mortality estimates for some of the cause-specific categories only but these inferences may only work within a country as the ratios vary substantially between nations.

Our seasonal all-cause excess mortality estimates for the United States for influenza seasons 2015/16 and 2016/17 were 15,068 deaths (10,582-19,558) and 46,292 deaths (42,047-50,540), respectively. The estimates for season 2015/16 were lower than the estimates published by the Centers for Disease Control and Prevention (CDC), while the estimates for season 2016/17 fell within the range of the estimates published by CDC of 23,000 deaths (17,000-35,000) for season 2015/16 and 38,000 deaths (29,000-61,000) for season 2016/17 (31). Our seasonal respiratory and circulatory excess mortality estimates for season 2015/16 and season 2016/17 were substantially lower at 5,425 (2,980-7,873) and 22,306 (20,173- 24,441), respectively. The CDC estimates influenza-associated deaths based on the number of laboratory-confirmed influenza-associated hospitalizations, which have been adjusted for under-detection of influenza. This is done by using a death to hospitalization ratio that represents the expected number of influenza deaths relative to the number of influenza-associated hospitalizations (6,31). In principle, using laboratory-confirmed influenza-associated hospitalizations may be an accurate way of approximating the true underlying mortality burden of influenza. In practice, however, it would have to adequately adjust for the fact that many elderly people may die without being hospitalized or tested first. In contrast, estimates based on all-cause excess mortality are expected to be an overestimate or, perhaps, an upper bound of the true underlying mortality burden (8). Given this, it is surprising that our all-cause excess mortality estimates were not considerably higher than the CDC estimates. One potential explanation for this might have been that we did not truncate negative excess values. However, as shown in Figure 1, the seasons we examined did not have periods where the observed mortality was considerably below the baseline. Furthermore, we generated seasonal estimates where negative values had been truncated (22,558 deaths and 48,421 deaths for the seasons 2015/16 and 2016/17, respectively). These estimates feel within the ranges of the estimates published by the CDC.

Our seasonal all-cause excess mortality estimates for Denmark for the 2015/16 and 2016/17 seasons were 20.3 (15.8-25.0) and 24.0 (19.3-28.7) per 100,000 population. They were around twice as high as the influenza mortality estimates published by the State Serum Institute (SSI) of 8.3 (7.1-9.5) and 13.04 (11.75-14.38) per 100,000 population, respectively (32). Our seasonal respiratory and circulatory excess mortality estimates at 9.4 (6.4-12.3) and 12.3 (9.3-15.4) per 100,000 population for the 2015/16 and the 2016/17 seasons were in agreement with the national estimates. SSI estimates influenza-associated deaths based on the FluMOMO model, which is a multivariable time series model with all-cause mortality as outcome and influenza activity and extreme temperatures as explanatory variables while adjusting for time trend and seasonality (5). Although influenza may lead to excess mortality in causes of death not contained in the respiratory and circulatory categories, it is not surprising that the estimates based on these two categories came closer to the official estimates, which includes laboratory-confirmed indicators of influenza-activity, than the estimates based on all-cause mortality (1,8,13).

Our seasonal all-cause excess mortality estimates for Spain for the 2015/16 and 2016/17 seasons were 22.9 (18.9-26.9) and 52.9 (49.1-56.8) per 100,000 population. They were around 3.5 and 1.5 times higher than the influenza mortality estimates reported by the CNE-ISCIII of 6.0 (5.4-6.6) and 30.6 (29.5-31.8) per 100,000 population, respectively (33). Our seasonal respiratory and circulatory excess mortality estimates were more

similar at 9.8 (7.5-12.1) and 29.3 (27.1-31.4) per 100.000 population for the 2015/16 and the 2016/17 seasons, respectively. Like SSI, CNE-ISCIII uses the FluMOMO model to estimate influenza-associated mortality.

It is unclear whether there is a constant proportionality between the cause-specific excess mortality estimates and all-cause excess mortality estimates. In Denmark, it seemed to be the case, which may be due to its small and homogenous population, whereas Spain and the United States only showed a limited proportionality across the two seasons. In the United States, P&I excess mortality accounted for approximately 10% of the all-cause excess mortality each season, although the all-cause excess estimates tripled between the two seasons, whereas the proportion due to respiratory excess mortality increased from 17% to 24%. This proportionality between P&I and all-cause excess mortality is consistent with the linear correlation observed by Simonsen et al., although their model suggested that P&I excess mortality made up around 25% of all-cause excess mortality (34). In addition to population size, differences in coding practices and underlying diseases in the population may also be an important part of the explanation. Furthermore, vaccination programs in different risk groups likely vary between countries. Although the pattern of circulating influenza types was similar between the countries, the vaccination programs, underlying immunity, and contact patterns in the population may vary.and result in differences in excess mortality. It would be interesting to explore the proportionality we have observed, in particular for Denmark, within the respective countries. If this proportionality withstands further scrutiny, it may allow countries to approximate cause-specific excess mortality, e.g., respiratory excess mortality, based on all-cause excess mortality and thus obtain timely cause-specific excess mortality estimates.

Our approach did have limitations. The EuroMOMO model was originally designed for all-cause mortality data. Furthermore, it does not include indicators of influenza-activity, which may lead to residual confounding in the form of attributing winter excess mortality that is, in fact, due to other factors (such as other respiratory viruses and temperature) than influenza (8–10). Finally, it is worth emphasizing the fact that we only analyzed data from three relatively similar countries in that they are all high-income countries with temperate climates.

This analysis does not settle the discussion on the differences and merits of using all-cause mortality data and cause-specific mortality data for estimating mortality related to influenza as it is notoriously difficult and purposes with the estimations may differ (14). On the one hand, all-cause excess mortality estimates can be made available weekly in many countries and seem to display a weekly pattern that suggests that all-cause excess mortality move proportionally to excess mortality of causes of death that is closely related to influenza (such as respiratory causes of death) within the periods typically associated with influenza. Furthermore, our all-cause excess mortality estimates approximated the influenza mortality burden estimates published by CDC, which are based on laboratory-confirmed hospitalizations (6,31). On the other hand, the proportionality between the seasonally cumulated all-cause excess mortality and the select cause-specific excess mortality estimates (such as P&I and respiratory) does not seem to be reliably constant across seasons within all three countries. Additionally, all-cause excess mortality estimates come with the risk of losing specificity and consequently overestimating the influenza mortality burden. This was indicated by the fact that our estimates for Denmark and Spain were between 1.5 and 3.5 times higher than the estimates produced by the FluMOMO model, which includes indicators of influenza-activity and temperature, whereas our respiratory and circulatory excess mortality estimates approximated the FluMOMO estimates (5,32,33). Moreover, cause-specific mortality data is increasingly available more quickly in some countries; for example, CDC has access to P&I mortality data on a weekly basis, and additional advances in the timeliness of data availability are likely to be gained from the ongoing pandemic (7).

In conclusion, using a simple model of all-cause excess mortality is a valuable tool for timely risk assessment of seasonal influenza and emerging threats such as the COVID-19 pandemic, as the data are readily available in many countries, and the approach is not sensitive to coding practices in cause-of-death-registers and collection of other indicators. To obtain precise estimates of excess mortality related to influenza, all-cause mortality data should be supplemented with cause-specific data and indicators of influenza transmission.

Acknowledgments

This study was conducted as part of Sebastian Schmidt's research fellowship, which was financially supported by the Novo Nordisk Foundation and A.P. Møller Fonden.

The EuroMOMO network has received financial support from the European Centre for Disease Prevention and Control (ECDC) and from the World Health Organization (WHO) Regional Office for Europe.

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Conflicts of interest

None declared.

Authors' contributions

Sebastian Schmidt drafted the first version of the manuscript and performed all analyses, graphs, and tables. The co-authors provided data, valuable feedback on the project as a whole, including the analytic approach, and by reviewing and contributing to drafting the manuscript.

References

1. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. The Lancet. 2018 Mar;391(10127):1285–300.

2. The 1918 Flu Pandemic: Why It Matters 100 Years Later | | Blogs | CDC [Internet]. [cited 2020 Feb 18]. Available from: https://blogs.cdc.gov/publichealthmatters/2018/05/1918-flu/

3. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. [cited 2020 May 11]. Available from: https://covid19.who.int/

4. Muscatello DJ, Newall AT, Dwyer DE, Macintyre CR. Mortality attributable to seasonal and pandemic influenza, Australia, 2003 to 2009, using a novel time series smoothing approach. PloS One. 2014;8(6):e64734.

5. Nielsen J, Krause TG, Mølbak K. Influenza-Associated Mortality Determined from All-Cause Mortality, Denmark 2010/11-2016/17: The Flumomo Model. Influenza Other Respir Viruses. 2018 Sep;12(5):591–604.

6. Reed C, Chaves SS, Kirley PD, Emerson R, Aragon D, Hancock EB, et al. Estimating Influenza Disease Burden from Population-Based Surveillance Data in the United States. PLOS ONE. 2015 Mar 4;10(3):e0118369.

7. U.S. Influenza Surveillance System: Purpose and Methods | CDC [Internet]. 2020 [cited 2020 May 11]. Available from: https://www.cdc.gov/flu/weekly/overview.htm

8. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality Associated With Influenza and Respiratory Syncytial Virus in the United States. :8.

9. van Asten L, van den Wijngaard C, van Pelt W, van de Kassteele J, Meijer A, van der Hoek W, et al. Mortality attributable to 9 common infections: significant effect of influenza A, respiratory syncytial virus, influenza B, norovirus, and parainfluenza in elderly persons. J Infect Dis. 2012 Sep 1;206(5):628–39.

10. Donaldson GC, Keatinge WR. Excess winter mortality: influenza or cold stress? Observational study. BMJ. 2002 Jan 12;324(7329):89–90.

11. EUROMOMO EuroMOMO Bulletin, Week 18, 2020 [Internet]. EUROMOMO. [cited 2020 May 11]. Available from: https://euromomo.eu/dev-404-page/

12. Warren-Gash C, Bhaskaran K, Hayward A, Leung GM, Lo S-V, Wong C-M, et al. Circulating influenza virus, climatic factors, and acute myocardial infarction: a time series study in England and Wales and Hong Kong. J Infect Dis. 2011 Jun 15;203(12):1710–8.

13. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. N Engl J Med. 2018 Jan 25;378(4):345–53.

14. Simonsen L, Viboud C. The Art of Modeling the Mortality Impact of Winter-Seasonal Pathogens. J Infect Dis. 2012 Sep 1;206(5):625–7.

15. Guidelines_Cause_of_Death_COVID-19.pdf [Internet]. [cited 2020 May 11]. Available from: https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19.pdf

16. Weinberger D, Cohen T, Crawford F, Mostashari F, Olson D, Pitzer VE, et al. Estimating the early death toll of COVID-19 in the United States [Preprint]. medRxiv. 2020 Apr 29;2020.04.15.20066431.

17. EUROMOMO EuroMOMO Bulletin, Week 19, 2020 [Internet]. EUROMOMO. 2020 [cited 2020 May 15]. Available from: https://euromomo.eu

18. Mazick A, Gergonne B, Nielsen J, Wuillaume F, Virtanen MJ, Fouillet A, et al. Excess mortality among the elderly in 12 European countries, February and March 2012. Eurosurveillance. 2012 Apr 5;17(14):20138.

19. Vestergaard LS, Nielsen J, Krause TG, Espenhain L, Tersago K, Bustos Sierra N, et al. Excess all-cause and influenza-attributable mortality in Europe, December 2016 to February 2017. Eurosurveillance [Internet]. 2017 Apr 6 [cited 2019 Aug 14];22(14). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5388126/

20. European All-Cause Excess and Influenza-Attributable Mortality in the 2017/18 Season: Should the Burden of Influenza B Be Reconsidered? | Elsevier Enhanced Reader [Internet]. [cited 2019 Aug 16]. Available from: https://reader.elsevier.com/reader/sd/pii/S1198743X19300588?token=52DC03010E9634B9A522D90A92672F7506749A4FC83E06F9AB33A4A3CDD5D89E6B291EC5624145B0BEA9D53E039498D2

21. ICD-10: International statistical classification of diseases and related health problems. Geneva: World Health Organization; 2011.

22. Home - Eurostat [Internet]. [cited 2020 May 17]. Available from: https://ec.europa.eu/eurostat/

23. Bureau UC. Census Data [Internet]. The United States Census Bureau. [cited 2020 May 11]. Available from: https://www.census.gov/topics/population/data.html

24. PAHO-Age-standardized-mortality-rates-2009.pdf [Internet]. [cited 2020 Feb 8]. Available from: https://www.paho.org/hq/dmdocuments/2012/PAHO-Age-standardized-mortality-rates-2009.pdf

25. Davlin SL. Influenza Activity — United States, 2015–16 Season and Composition of the 2016–17 Influenza Vaccine. MMWR Morb Mortal Wkly Rep [Internet]. 2016 [cited 2020 Jun 16];65. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6522a3.htm

26. Blanton L. Update: Influenza Activity in the United States During the 2016–17 Season and Composition of the 2017–18 Influenza Vaccine. MMWR Morb Mortal Wkly Rep [Internet]. 2017 [cited 2020 Jun 16];66. Available from: https://www.facebook.com/CDCMMWR

27. Centro Nacional de Epidemiología, Instituto de Salud Carlos III. annual influenza surveillance reports. :31.

28. Centro Nacional de Epidemiología, Instituto de Salud Carlos III. annual influenza surveillance reports. :32.

29. Statens Serum Institut. Uge 24 - 2016 [Internet]. [cited 2020 Jun 16]. Available from: https://www.ssi.dk/aktuelt/nyhedsbreve/epi-nyt/2016/uge-24---2016

30. Statens Serum Institut. Uge 24 - 2017 [Internet]. [cited 2020 Jun 16]. Available from: https://www.ssi.dk/aktuelt/nyhedsbreve/epi-nyt/2017/uge-24---2017

31. CDC. Burden of Influenza [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 Apr 23]. Available from: https://www.cdc.gov/flu/about/burden/index.html

32. Statens Serum Institut. Influenzasæsonen - opgørelse over sygdomsforekomst 2017/18 [Internet]. [cited 2020 Apr 23]. Available from: https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsovervaagning/i/influenzasaesonen---opgoerelse-over-sygdomsforekomst-2017-18

33. Mazagatos-Ateca C, Silva SP, Delgado-Sanz C, Rodrigues AP, Oliva J, Nunes B, Larrauri A. Influenza-attributable mortality in the Iberian Peninsula, seasons 2012/13 - 2017/18 [abstract]. In Reunion Cientifica de la Sociedad Espanola de Epidemiologia Y XIII Congresso da Associacao Portuguesa de Epidemiologia: 2018 Sep 11-14: Lisbon: Gaceta Sanitaria; 2018. p. Abstract nr 997.

34. Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health. 1997 Dec;87(12):1944–50.