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ORIGINAL RESEARCH

Influenza-Associated Excess Mortality and Hospitalization in Germany from 1996 to 2018

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ABSTRACT

Introduction: Influenza-associated excess mortality and morbidity is commonly estimated using statistical methods. In Germany, the Robert Koch Institute (RKI) uses the relative mortality distribution method (RMDM) to estimate influenza-associated excess mortality without reporting age-specific values. In order to better differentiate the distribution of the disease burden, a distinction by age is of high relevance. Therefore, we aimed to revise the existing excess mortality model and provide age-specific excess mortality estimates over multiple seasons. We also used the model to determine influenza-associated excess hospitalizations, since the RKI excess hospitalization model is currently based on another approach (i.e., combination of excess physician visits and hospitalized proportion).
Methods: This study was a retrospective data analysis based on secondary data of the German population from 1996–2018. We adapted the RKI's method of estimating influenza-associated excess mortality with the RMDM and also applied this approach to excess hospitalizations. We calculated the number of excess deaths/hospitalizations using weekly and age-specific data.
Results: Data available in Germany are suitable for addressing the restrictions of the RKI's mortality model. In total, we estimated 175,858 (176,482 with age stratification) influenza-associated excess all cause deaths between 1995–1996 and 2017–2018 ranging from 0 (17 with age stratification) in 2005–2006 to 25,599 (25,527 with age stratification) in 2017–2018. Total influenza-associated excess deaths were comparable to RKI's estimates in most seasons. Most excess

Prior Presentation: Partial results have already been presented as a poster at the 8th ESWI (European Scientific Working Group on Influenza) Influenza Conference (4–7 December 2021; Online conference). The abstract book is openly available at https://s3.eu-central-1.amazonaws.com/eswi.org/downloads/8EIC_abstractbook_04122021.pdf.

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deaths/hospitalizations occurred in patients aged ≥ 60 years (95.42%/57.49%) followed by those aged 35–59 years (3,80%/24,98%). Compared with our model, the RKI hospitalization model implies a substantial underestimation of excess hospitalizations (828,090 vs. 374,200 over all seasons).
Conclusion: This is the first study that provides age-specific estimates of influenza-associated excess mortality in Germany. The results clearly show that the main burden of influenza is in the elderly, for whom prevention and control measures should be prioritized.

Keywords: Influenza; Human; Excess mortality; Hospitalization; Patient admission; Germany

Key Summary Points

Every season, influenza causes substantial morbidity and mortality across all age groups, which can only be determined using statistical methods.

In Germany, influenza-associated excess mortality is determined by the Robert Koch Institute (RKI) but without age-specific values, which are highly relevant for understanding the distribution of the disease burden.

Using age-specific data indicates that most excess deaths occurred in patients aged ≥ 60 years (i.e., 95.46%).

Most excess hospitalizations occurred in patients aged ≥ 60 years (i.e. 57.49%). However, the impact of hospitalizations in those aged 18–59 years (i.e. 32,96%) should not be neglected.

This clearly shows that the main burden of influenza-associated mortality is in the elderly, while influenza-associated hospitalizations also largely affect the working population and are potentially responsible for many disabilities.

INTRODUCTION

Influenza is a vaccine-preventable disease which causes substantial morbidity and mortality across all age groups, with the severity of the disease burden varying from season to season. The Burden of Communicable Diseases in Europe (BCoDE) 2009–2013 study, which was conducted before the COVID-19 pandemic, used the disability-adjusted life year (DALY) as a key outcome measure. The study found that, of all infectious diseases, influenza has the greatest impact on health in the European Union and European Economic Area [1]. Influenza infection leads not only to acute respiratory illness but also to extra-pulmonary complications (e.g., cardiovascular events), an aspect of the disease burden often overlooked [2–5].

Although mortality contributes substantially to influenza's public health burden, quantifying the number of deaths is challenging; as influenza is rarely confirmed by virologic testing, it is consequently rarely reported as an underlying cause of death. This leads to substantially inaccurate influenza-related mortality data and, most importantly, to an underestimation of influenza's impact on deaths [6–9].

To overcome these obstacles, influenza-associated mortality and morbidity is commonly estimated using statistical methods [9, 10]. According to Li et al. [10], these methods can be distinguished mainly by their use of a proxy for influenza activity. The first group incorporates this proxy into generalized linear models for prediction. The most commonly used proxies include the proportions or numbers of laboratory samples that test positive for influenza [11–14], ambulatory consultations for influenza-like illness [15], or a combination of both [16, 17]. The group without a proxy can be roughly divided into three categories. First, there is the group of so-called serfling-type models [18–22], which use regression models with Fourier terms. Another group uses non-serfling regressions [23, 24]. Besides regression use, the moving average method [25], or the relative mortality distribution model [6], are also methods without a proxy.

Total excess death figures without age differentiation have been reported for Germany by the German public health institute (Robert Koch Institute; RKI) for many years. For this purpose, the RKI uses a simple approach based on the annual distribution of monthly relative mortality (relative mortality distribution method; RMDM) applied to a time series of monthly all-cause mortality data in Germany [6, 26, 27] (see Methods). In most seasons, both a crude and a conservative (an uncertainty interval is subtracted) estimate are calculated. So far, this method has relied on monthly aggregate death figures without age stratification. However, age stratification would help decision-makers target the age groups most impacted by excess mortality, with intensified prevention measures. The elderly are more susceptible to influenza infection and are at increased risk of developing serious complications [28]. With 28.16% of the German population aged ≥ 60 in 2018 [29]—a number likely to increase in the future—targeting influenza prevention to these groups is especially important. In addition, using weekly instead of monthly data would improve accuracy, especially for the identification of an influenza wave, while a distinction according to the cause of death would provide further insights.

The aim of this study is to overcome the previously described limitations of the existing excess mortality model by using weekly death data stratified by age and cause of death, and to update the estimated influenza-associated excess mortality and hospitalization estimates from 1996 to 2018.

METHODS

Study Design

This is a retrospective secondary data analysis of the German population from 1996 to 2018. We merged different datasets on influenza activity, deaths, and hospitalizations, using weekly and age-specific data to calculate the number of all-cause influenza-associated excess deaths/hospitalizations, as well as excess values stratified by age group and cause of death. The RMDM first determines the average proportion of a calendar week in the respective annual mortality over the entire period. Thereby, only weeks without influenza activity are used. The expected mortality (without influenza in the background) of a week can then be calculated by multiplying the average weekly share by the corresponding annual mortality. Subsequently, the excess mortality in the weeks with influenza activity can be estimated by subtracting the expected mortality from the mortality that actually occurred.

Data Sources

To identify influenza activity periods, the duration (in weeks) of each influenza season in Germany between 1996 and 2018 was gathered from annually published influenza surveillance reports from the RKI influenza working group [32] and from the weekly epidemiological bulletin published by the RKI [33]. From 2008 to 2009 onwards, the reports directly present influenza activity; prior to this, it could be accurately deduced by combining both sources.

The weekly number of age-specific all-cause hospital admissions and deaths throughout Germany from 1996 to 2018 were obtained from the Research Data Centre of the Federal Statistical Office, and the Statistical Offices of the Federal States (FDZ), which offer a range of data and services for the scientific use of microdata from national statistics [34, 35]. Extracted mortality data also included the cause of death.

Data on population size and the corresponding age structure in the study period were taken from official demographic statistics of The Federal Statistical Office (Destatis) [29].

These datasets were merged using combinations of the respective years and weeks.

No formal ethical approval was required as no primary collection of individual human data occurred and only anonymized healthcare data were used. The used data from the RKI and Destatis are openly available, while the data from the FDZ required permission. No patient consent was necessary as no primary collection of individual human data occurred and only anonymized healthcare data were used.

Age Groups

In a model without age stratification, the number of total deaths and hospitalizations in older people overshadows any smaller deviations in younger people, leaving excess deaths and hospitalizations in younger individuals undetected. Therefore, we performed all analyses on four age groups (0–17, 18–34, 35–59, ≥ 60 years), in addition to a model without age stratification. To allow a direct comparison with the publications of the RKI, we tried to use the same age groups. The choice of the limit at 60 years is based on the recommendation of the Standing Committee on Vaccination (STIKO) at the RKI, which recommends influenza vaccination from the age of 60 [36]. For a more detailed excess mortality analysis in the ≥ 60 years age group, we further refined this group into four age groups (60–69, 70–79, 80–89, and ≥ 90 years).

Mortality Outcome Categories

We used various outcome categories based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) that have previously been considered in excess mortality studies from other countries [10, 12, 14, 37]. These include pneumonia and influenza (P&I; ICD-10 codes J09–J18), diseases of the respiratory system (ICD-10 codes J00–J99), diseases of the circulatory system (ICD-10 codes I00–I99), diseases of the circulatory and respiratory system (cardiorespiratory diseases; ICD-10 codes I00–I99 and J00–J99) and all-cause (ICD-10 codes A00-Z99). With these categories, we covered the entire range of sensitivity and specificity, with all-cause being the broadest outcome definition, but lacking specificity, and P&I being the most specific one, but not encompassing all influenza-related deaths [10–12]. Due to changes in the ICD system in Germany (switch from ICD-9 to ICD-10), cause of death stratification was only applied from 1998.

Statistical Analysis

Influenza-associated excess numbers are defined as the difference between numbers observed during influenza weeks and expected numbers based on weeks in the absence of an influenza wave (baseline). Similar to the RKI, we used the RMDM to calculate the baseline [6]. First, the average deaths/hospitalizations per calendar week were determined if the total deaths/hospitalizations in a year were evenly distributed across all weeks. Then, the actual deaths/hospitalizations were compared to the previously calculated average in each week of the year, which reflects the distribution of the ratio of weekly deaths/hospitalizations to weekly average deaths/hospitalizations (i.e., relative mortality/hospitalization). The RMDM relies on the fact that this distribution is fairly constant across all observed years, with higher values in the winter and lower values in the summer [6] (see also Fig. 1) So, each week has a fairly constant share of annual mortality/hospitalizations across the years. According to Zucs et al. [6], the share of each week in the total deaths/hospitalizations of a year was determined for all years and thus the average relative weekly share across all years was obtained. Multiplying this weekly average by the respective annual deaths/hospitalizations gives the expected deaths/hospitalizations for each week. However, the baseline calculated in this way still contains influenza. In order to estimate baseline mortality without influenza, weeks with elevated influenza activity and simultaneously more deaths/hospitalizations observed than expected (model values) were excluded now. By minimizing the residuals for the remaining weeks, average weekly shares were recalculated. This was repeated a second time to produce a final baseline mortality/hospitalization model. Finally, excess deaths/hospitalizations were calculated by subtracting the expected baseline from the observed deaths/hospitalizations. Seasonal excess deaths/hospitalizations were defined as the seasonal sum of positive weekly excess deaths/hospitalizations. These steps were repeated for subsamples, stratified by age and reported cause of death.

Following the approach by RKI, a conservative estimate was obtained by subtracting one standard deviation of the differences (residuals) between modeled and observed values of the influenza-free weeks [38]. We calculated the upper and lower 90% confidence interval (CI)

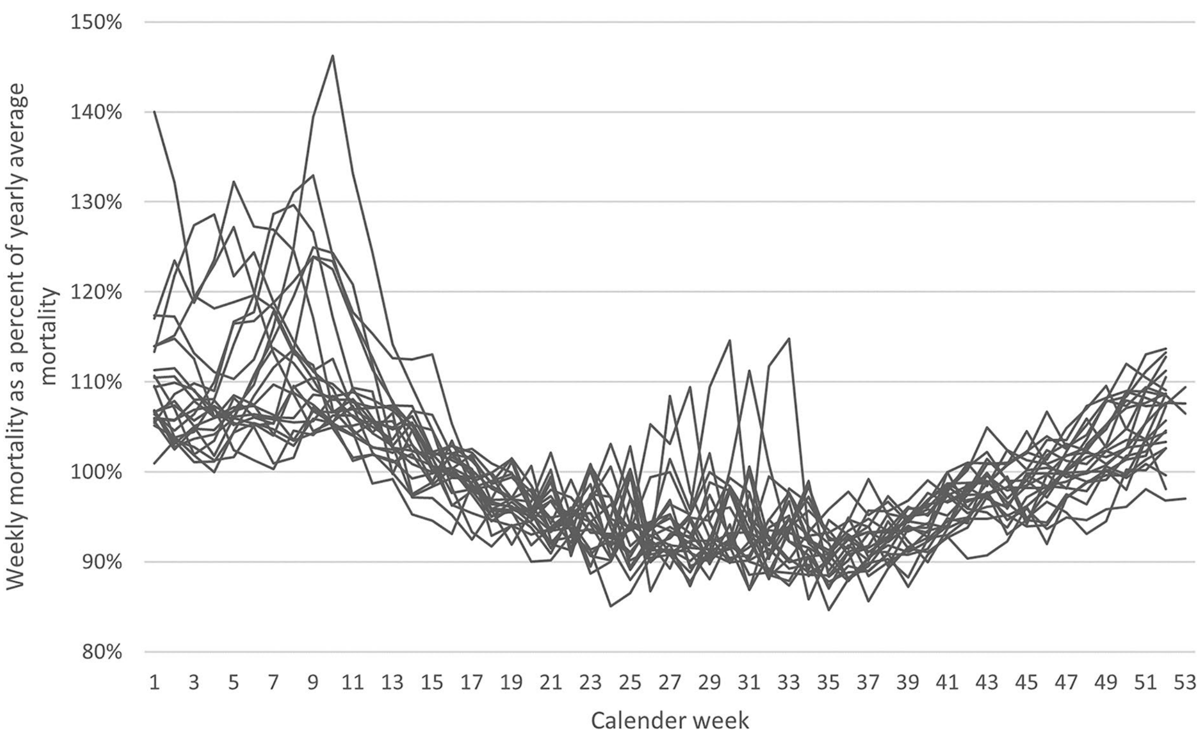

Fig. 1 Annual distribution of weekly all-cause mortality relative to the yearly average mortality for 1996–2018

for all values analogous to the RKI [6]. Analyses were conducted using Microsoft SQL Server Management Studio (17.4) and SAS (3.8).

RESULTS

Descriptive Statistics of Data Used for Modeling

Between 1996 and 2018, the German population increased from 82.01 to 83.02 million. In 1996, 21.41% of the population was aged ≥ 60, increasing to 28.16% in 2018. 34.77% to 37.69% were aged 35–59 years, the age group to which the largest proportion of the population belonged. In total, between 819,226 and 952,294 people died annually (all causes). While the number of people who died from circulatory diseases decreased from 415,010 (47.85% of all deaths) in 1998 to 344,190 (36.14%) in 2018, the number of people who died from respiratory diseases and P&I increased from 49,607 (5.72%) and 17,641 (2.03%) in 1998, to 71,479 (7.51%) and 23,126 (2.43%) in 2018, respectively. Hospital admissions showed a similar pattern, ranging from 15,957,603 to 20,017,801 annual hospitalizations during the study period. This corresponds to an increase of 22.50% from 1996 to 2018.

Model Characteristics (Distribution of Weekly Data and Comparison of Observed vs. Expected Values)

The variation of weekly mortality in relation to the respective average weekly mortality throughout the year remained fairly constant across all observed years (Fig. 1). A similar pattern was observed in the hospitalization model (see supplementary material Figure S1).

Figure 2 displays observed and expected mortality by week. Excess mortality is displayed by the (shaded) area between the lines. Figure S2 (see supplementary material) shows the rates for the hospitalization model.

Estimated Influenza-Associated Excess Deaths

The conservative estimates of influenza-associated excess all cause deaths, with and without age differentiation, compared to RKI values (1995–1996 to 2000–2001 [39]; 2001–2002 to 2017–2018 [31]), are presented in Table 1. In total, we estimated 175,858 (176,482 with age stratification) influenza-associated excess all cause deaths between 1995–1996 and 2017–2018, with 25,999 (25,527) being from the most recent season (2017–2018). Estimated excess deaths are in line with RKI's estimates in most years. For the first seasons in the study period (from 1995–1996 to 1997–1998), our estimate differed due to database differences in databases (RKI used data from 1988 onward). The most significant difference occurred in the 2014–2015 season, when RKI estimated about 6000 more deaths than our model. Excess mortality increased with age with most influenza-related deaths occurring in those aged ≥ 60 years (approximately 95% across all seasons). Table 2 shows the same results as mortality rates per 100,000 population.

To further examine the impact of influenza on the elderly (aged ≥ 60 years), we divided this group into four subgroups. The conservative excess mortality results for these groups are displayed in Fig. 3. See supplementary material Table S1 for corresponding data.

Influenza had the greatest impact on the elderly aged 80–89 years. Across all seasons, 43.19% of all deaths among people aged ≥ 60 years were in those aged 80–89 years, followed by those aged ≥ 90 years (27.37%). About one-fifth of deaths in the age group ≥ 60 years were those aged 70–79 years (21.32%).

Further insights are provided by the estimated influenza-associated excess deaths when detailed by cause of death (Fig. 4; supplementary material Table S2).

Due to changes in the ICD catalogue, a distinction by cause of death could be carried out

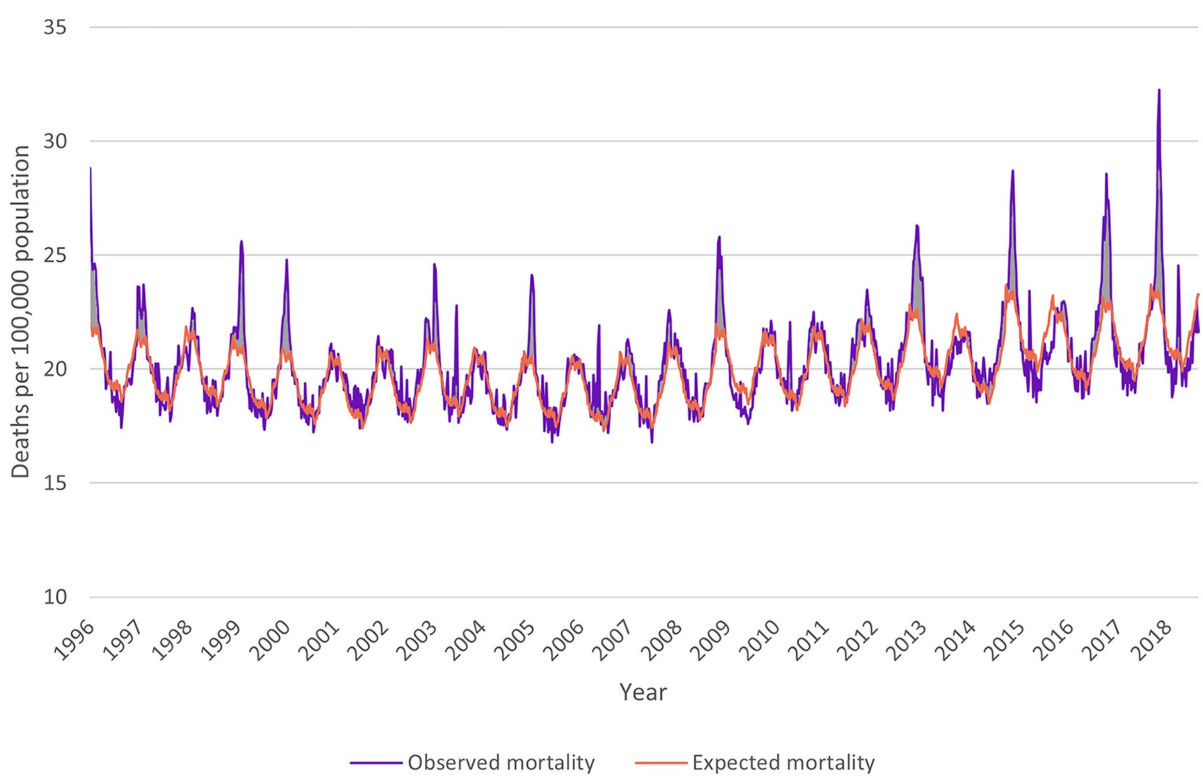

Fig. 2 Weekly comparison of observed vs. expected death

Table 1 Cumulated influenza-associated excess all-cause deaths (90% CI) during the winter season in Germany, by age group, 1996–2018

Season	RKI[a]	Without age groups	Age groups				
			0–17	18–34	35–59	≥ 60	All ages
1995–1996	25,000	18,753 (16,219; 21,316)	50 (0; 254)	133 (14; 366)	658 (129; 1538)	17,968 (15,611; 20,353)	18,809 (16,269; 21,378)
1996–1997	8700	2236 (1623; 2856)	47 (19; 107)	2 (0; 72)	146 (0; 362)	2058 (1489; 2635)	2254 (1639; 2876)
1997–1998	3900	1486 (462; 3309)	50 (6; 235)	0 (0; 200)	67 (0; 723)	1503 (534; 3126)	1620 (508; 3770)
1998–1999	15,100	14,917 (12,396; 17,987)	24 (0; 260)	14 (0; 235)	332 (50; 1202)	14,564 (12,134; 17,413)	14,934 (12,351; 18,037)
1999–2000	12,700	11,036 (9194; 12,900)	20 (0; 153)	45 (0; 246)	568 (164; 1177)	10,344 (8620; 12,090)	10,977 (9131; 12,845)
2000–2001	0	184 (0; 483)	5 (0; 56)	0 (0; 69)	0 (0; 236)	206 (0; 487)	212 (0; 1111)
2001–2002	0	1049 (458; 2201)	21 (0; 203)	22 (0; 226)	127 (0; 757)	914 (360; 2020)	1084 (416; 3791)
2002–2003	8000	6619 (5088; 8169)	16 (0; 175)	35 (0; 242)	281 (13; 890)	6233 (4791; 7694)	6565 (5030; 9031)
2003–2004	0	360 (0; 1043)	19 (0; 180)	26 (0; 225)	0 (0; 219)	447 (61; 1140)	491 (43; 2893)
2004–2005	11,700	11,555 (9442; 13,709)	24 (0; 179)	0 (0; 163)	267 (0; 923)	11,367 (9369; 13,408)	11,657 (9527; 14,118)
2005–2006	0	0 (0; 256)	13 (0; 172)	4 (0; 186)	0 (0; 605)	0 (0; 274)	17 (0; 3271)
2006–2007	200	1486 (101; 3279)	2 (0; 160)	32 (0; 259)	72 (0; 723)	1387 (108; 3078)	1492 (74; 4189)
2007–2008	900	390 (0; 1083)	7 (0; 156)	15 (0; 158)	88 (0; 721)	348 (0; 1019)	458 (0; 2875)

Table 1 continued

Season	RKI[a]	Without age groups	Age groups				
			0–17	18–34	35–59	≥ 60	All ages
2008–2009	18,800	15,206 (12,208; 19,455)	47 (0; 271)	37 (0; 236)	341 (16; 1464)	14,898 (12,001; 18,944)	15,323 (12,215; 19,990)
2009–2010	0	0 (0; 0)	31 (0; 200)	34 (0; 320)	200 (8; 921)	0 (0; 0)	265 (0; 4514)
2010–2011	0	1838 (360; 4626)	44 (0; 351)	58 (0; 434)	183 (0; 1488)	1674 (265; 4288)	1960 (309; 7129)
2011–2012	2400	2306 (1028; 4816)	4 (0; 184)	21 (0; 197)	62 (0; 837)	2149 (988; 4643)	2237 (1004; 5599)
2012–2013	20,700	21,237 (16,760; 26,032)	43 (0; 345)	88 (0; 530)	885 (142; 2525)	19,976 (15,724; 24,513)	20,991 (16,507; 26,982)
2013–2014	0	170 (0; 983)	5 (0; 93)	18 (0; 156)	0 (0; 385)	156 (0; 925)	179 (0; 2315)
2014–2015	21,300	14,988 (12,384; 17,761)	19 (0; 238)	22 (0; 285)	310 (11; 1060)	14,703 (12,227; 17,470)	15,053 (12,443; 19,903)
2015–2016	0	518 (0; 1935)	24 (0; 234)	71 (0; 367)	311 (0; 1376)	177 (0; 1363)	583 (0; 4963)
2016–2017	22,900	23,925 (20,363; 27,527)	34 (0; 271)	57 (0; 374)	496 (51; 1569)	23,209 (19,803; 26,656)	23,796 (20,212; 28,043)
2017–2018	25,100	25,599 (22,948; 28,415)	29 (0; 297)	67 (0; 421)	1318 (724; 2281)	24,113 (21,575; 26,868)	25,527 (22,821; 30,465)

[a] *RKI* Robert Koch Institute

Table 2 Cumulated influenza-associated excess all-cause mortality per 100,000 population (90% CI) during the winter season in Germany, by age group, 1996–2018

Season	RKI[a]	Without age groups	Age groups				
			0–17	18–34	35–59	≥ 60	All ages
1995–1996	30.48	22.87 (19.78; 25.99)	0.32 (0; 1.6)	0.66 (0.07; 1.83)	2.31 (0.45; 5.4)	102.35 (88.92; 115.94)	22.93 (19.84; 26.07)
1996–1997	10.60	2.72 (1.98; 3.48)	0.3 (0.12; 0.67)	0.01 (0; 0.37)	0.51 (0; 1.26)	11.48 (8.3; 14.7)	2.75 (2; 3.5)
1997–1998	4.75	1.81 (0.56; 4.03)	0.32 (0.04; 1.49)	0 (0; 1.05)	0.23 (0; 2.5)	8.18 (2.91; 17.02)	1.97 (0.62; 4.6)
1998–1999	18.38	18.16 (15.09; 21.89)	0.15 (0; 1.66)	0.07 (0; 1.26)	1.14 (0.17; 4.14)	77.14 (64.27; 92.22)	18.18 (15.03; 21.95)
1999–2000	15.44	13.42 (11.18; 15.68)	0.13 (0; 0.99)	0.25 (0; 1.35)	1.95 (0.56; 4.03)	53.28 (44.4; 62.28)	13.34 (11.1; 15.61)
2000–2001	0	0.22 (0; 0.59)	0.03 (0; 0.37)	0 (0; 0.39)	0 (0; 0.8)	1.04 (0; 2.45)	0.26 (0; 1.35)
2001–2002	0	1.27 (0.55; 2.67)	0.14 (0; 1.33)	0.12 (0; 1.29)	0.43 (0; 2.54)	4.55 (1.79; 10.05)	1.31 (0.5; 4.59)
2002–2003	9.69	8.02 (6.16; 9.9)	0.1 (0; 1.17)	0.2 (0; 1.41)	0.94 (0.04; 2.96)	30.65 (23.56; 37.84)	7.95 (6.09; 10.94)
2003–2004	0	0.44 (0; 1.26)	0.13 (0; 1.21)	0.15 (0; 1.34)	0 (0; 0.72)	2.17 (0.3; 5.55)	0.6 (0.05; 3.51)
2004–2005	14.19	14.02 (11.45; 16.63)	0.16 (0; 1.23)	0 (0; 0.98)	0.87 (0; 3.01)	55.34 (45.61; 65.28)	14.14 (11.56; 17.13)
2005–2006	0	0 (0; 0.31)	0.09 (0; 1.21)	0.02 (0; 1.12)	0 (0; 1.96)	0 (0; 1.33)	0.02 (0; 3.97)
2006–2007	0.24	1.81 (0.12; 3.99)	0.01 (0; 1.14)	0.19 (0; 1.57)	0.23 (0; 2.33)	6.68 (0.52; 14.82)	1.81 (0.09; 5.09)
2007–2008	1.10	0.48 (0; 1.32)	0.05 (0; 1.14)	0.09 (0; 0.96)	0.29 (0; 2.34)	1.66 (0; 4.86)	0.56 (0; 3.51)

Table 2 continued

Season	RKI[a]	Without age groups	Age groups				
			0–17	18–34	35–59	≥ 60	All ages
2008–2009	22.98	18.59 (14.92; 23.78)	0.35 (0; 2.01)	0.23 (0; 1.43)	1.11 (0.05; 4.78)	70.24 (56.58; 89.32)	18.73 (14.93; 24.44)
2009–2010	0	0 (0; 0)	0.23 (0; 1.5)	0.21 (0; 1.93)	0.66 (0.03; 3.03)	0 (0; 0)	0.32 (0; 5.52)
2010–2011	0	2.29 (0.45; 5.76)	0.34 (0; 2.67)	0.36 (0; 2.69)	0.62 (0; 5.03)	7.81 (1.24; 20)	2.44 (0.38; 8.88)
2011–2012	2.98	2.86 (1.28; 5.98)	0.03 (0; 1.41)	0.13 (0; 1.21)	0.21 (0; 2.84)	9.9 (4.55; 21.39)	2.78 (1.25; 6.95)
2012–2013	25.63	26.29 (20.75; 32.23)	0.33 (0; 2.63)	0.54 (0; 3.25)	3.01 (0.48; 8.58)	91.01 (71.64; 111.69)	25,99 (20,44; 33,41)
2013–2014	0	0.21 (0; 1.21)	0.04 (0; 0.71)	0.11 (0; 0.95)	0 (0; 1.31)	0.7 (0; 4.16)	0,22 (0; 2,85)
2014–2015	25.92	18.24 (15.07; 21.61)	0.14 (0; 1.78)	0.13 (0; 1.69)	1.05 (0.04; 3.6)	65.34 (54.34; 77.64)	18,32 (15,14; 24,22)
2015–2016	0	0.63 (0; 2.34)	0.18 (0; 1.74)	0.42 (0; 2.17)	1.06 (0; 4.69)	0.77 (0; 5.98)	0,71 (0; 6,01)
2016–2017	27.66	28.9 (24.6; 33.25)	0.25 (0; 2)	0.34 (0; 2.21)	1.7 (0.18; 5.36)	100.54 (85.78; 115.47)	28,74 (24,41; 33,87)
2017–2018	30.23	30.84 (27.64; 34.23)	0.21 (0; 2.19)	0.4 (0; 2.49)	4.52 (2.48; 7.83)	103.14 (92.29; 114.93)	30,75 (27,49; 36,7)

[a] *RKI* Robert Koch Institute

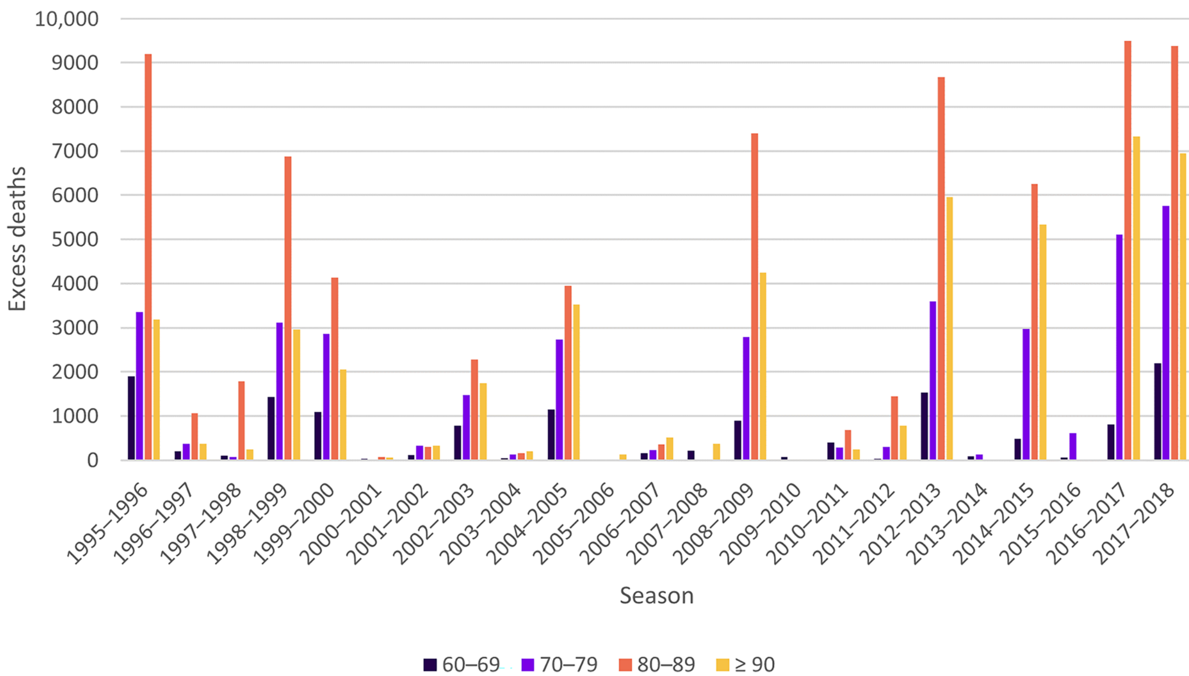

Fig. 3 Influenza-associated excess all-cause deaths in the population ≥ 60 years

beginning only from the 1998–1999 season. For this period, we calculated 153,383 influenza-associated all-cause, 113,306 (73.87% compared to all-cause) cardiorespiratory, 74,792 (48.76%) circulatory, 39,542 (25.78%) respiratory and 18,636 (12.15%) P&I excess deaths.

Estimated Influenza-Associated Excess All-Cause Hospitalizations

Tables S3 and S4 (see supplementary material) show the conservative estimates for excess all-cause hospitalizations and demonstrate a potential underestimation of the RKI's estimates compared to our model. In the study period, we estimated 828,090 excess hospitalizations, which is more than double the RKI's number (374,200). In the most recent 2017–2018 season, we estimated 70,455 (156.57% in comparison to the RKI) excess hospitalizations.

The main results with age differentiation are shown in Fig. 5. The biggest impact (57.49% of all excess hospitalizations) was in those aged ≥ 60 years, with 560,109 excess influenza-associated hospitalizations. The impact in the 2017–2018 season was even higher, with 73.24% of all excess hospitalizations being in patients aged ≥ 60 years.

DISCUSSION

We updated influenza-associated excess mortality and hospitalization estimates in Germany for all seasons from 1995–1996 to 2017–2018 using weekly data and investigating potential patterns in age and cause (for mortality only). The publicly available data from the FDZ and the RKI influenza working group appear to be suitable for addressing the limitations in the RKI's mortality model named by the RKI itself. Our model estimates aim to complement RKI's results, by providing an additional level of detail needed for medical decision-making. We found similar excess death results using weekly instead of monthly death figures. Our conservative model calculated an annual weighted average of approximately 7600 (9.32 per 100,000 population) compared to RKI's 8500 (10.46 per

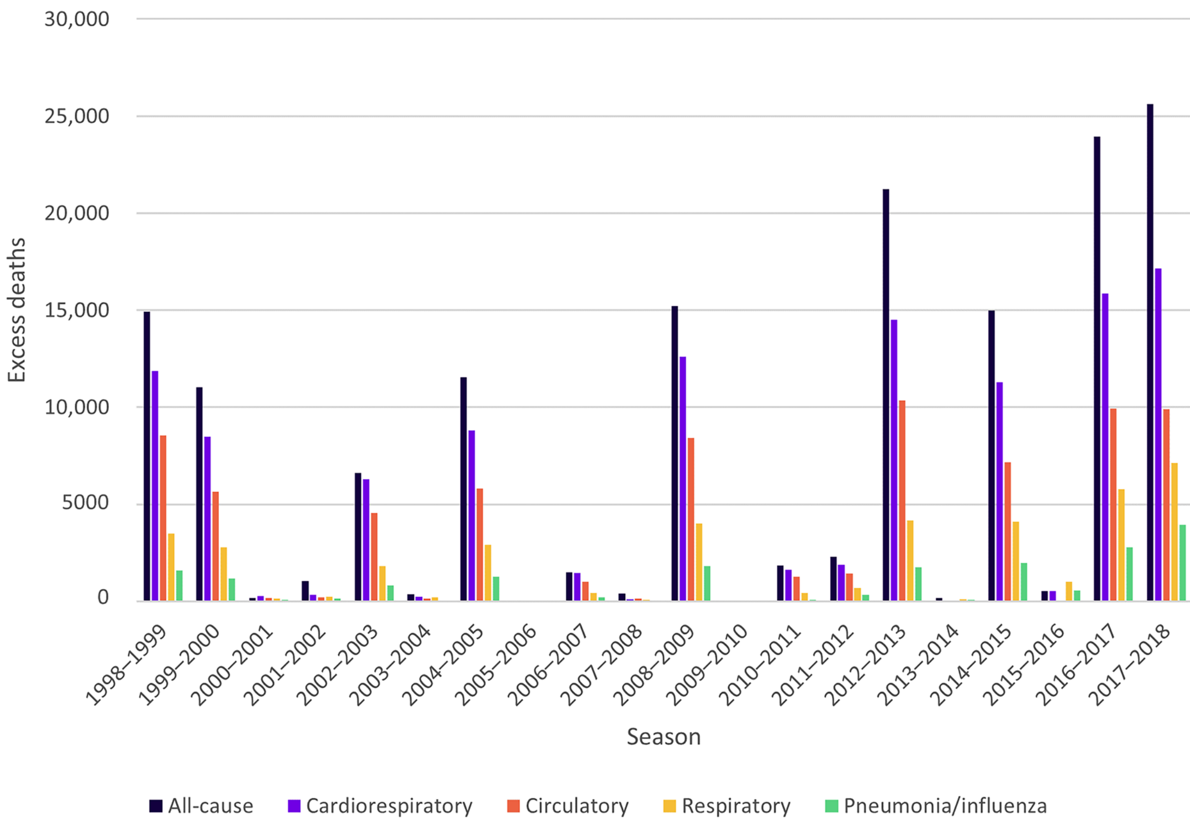

Fig. 4 Influenza-associated excess deaths using various mortality definitions

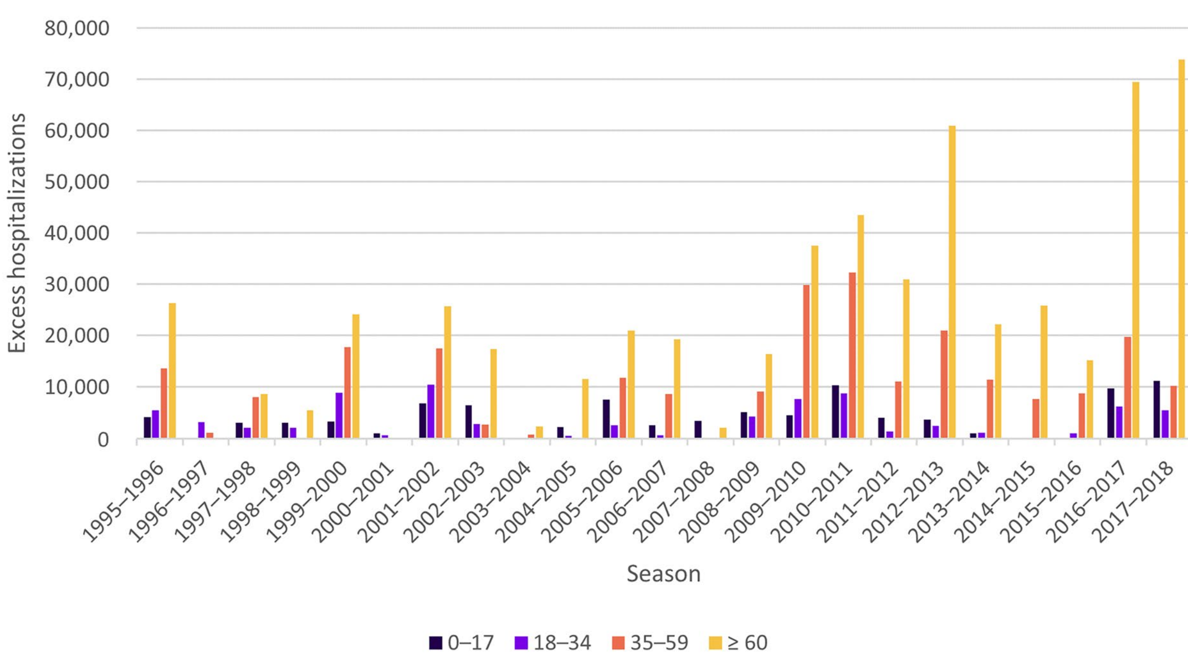

Fig. 5 Influenza-associated excess all-cause hospitalizations by age groups

100,000; self-calculated average [32]) excess all-cause deaths. On average, more than 95% of estimated excess mortality occurs in those aged ≥ 60 years (7300; 35.25 per 100,000) and, within this group, more than 43% of these excess deaths occurred in patients 80–89 years (3200; 95.40 per 100,000). The estimated annual average excess mortality from 1998–1999 through 2017–2018 across all ages was around 3700 deaths (4.56 per 100,000), 2000 (2.41 per 100,000), and 900 (1.14 per 100,000) with underlying circulatory, respiratory, or P&I cause, respectively.

In general, there are considerable differences in the statistical methods used in various studies to assess influenza-associated mortality and the results vary widely, with estimates increasing with age [10]. The systematic review from Li et al. [10] found values between – 0.3 to 1.3, 0.6–8.3 and 4–119 respiratory deaths per 100,000 population for the different age groups, defined as children, adults, and older adults. Our values (0.18 per 100,000 (0–17 years), 0.70 per 100,000 (18–59 years), and 35.25 per 100,000 (≥ 60 years)) are in line with this and thus confirm the results found there.

We estimated an annual average of around 36,000 (43.90 per 100,000) excess hospitalizations attributed to influenza, compared to RKI's 17,000 (20.74 per 100,000) hospital admissions. This suggests a potential, yet important, underestimation of the RKI model, due to their methodological approach. Influenza-associated excess hospitalization in Germany is estimated based on data from a surveillance system that monitors medically-attended acute respiratory infections (MAARI) in primary care practices. This involves two steps: first, excess consultations in Germany are estimated using a generalized additive regression model (GAM), with the age-specific weekly MAARI rate as a dependent variable [13, 30], then, second, the proportion of hospital admissions of all MAARI from the surveillance are determined and multiplied by the number of excess consultations, resulting in estimated excess hospitalization [30, 31]. We believe this two-step approach has a major limitation. The surveillance data come from office-based physicians; however, many referrals are not made by the general practitioners themselves, but rather by an on-call emergency physician or in the emergency room of a hospital. Therefore, the use of the proportion of hospital admissions among all MAARI may substantially underestimate influenza-related hospitalization burden as shown here. As in the mortality model, excess hospitalizations affect those aged ≥ 60 years most, with 57.49% of excess hospitalizations in this age group (24,300; 117.26 per 100,000). 32.96%, or around one-third, of all excess hospitalizations occurred in patients aged 18–59 (13,900; 29.74 per 100,000), which also has a major impact on the economy and should not be neglected. In Germany, the RKI estimates that 5.3 million people were unable to work due to influenza in 2017–2018, with the highest proportion in patients aged 35–59 at 2.9 million [40].

Our results clearly show that the main burden of influenza is in the elderly. For years, an influenza vaccination coverage rate of 75% and higher has been called for worldwide [41], and especially in the EU [42], for this group. However, current data show [43] that, in 2022, the rate for those aged ≥ 60 years in Germany was 43.30%, falling far short of the target.

Influenza's burden varies by season, which is likely related to variations in circulating viruses, vaccine effectiveness, and annual influenza epidemic timing. We found the lowest excess all-cause mortality occurred in 2005–2006 and 2009–2010, and the highest in 2016–2017 and 2017–2018. In contrast, excess all-cause hospitalization rates were lowest in 1998–1999, 2000–2001, and 2007–2008, and highest in 2010–2011 and 2016–2017.

Unlike most other methods, the RMDM does not use regressions, but relies solely on the recurrent relative mortality distribution pattern. It does not require a certain number of observations and does not use a proxy for influenza activity. Compared to other much more complex models, it is comparatively simple, practical, and does not need advanced mathematical expertise. A current internationally applied example of regression models with an influenza activity proxy is the FluMOMO model [16, 17, 37]. It is a time series regression model using a Poisson distribution, with correction for overdispersion, and includes influenza activity and extreme temperature as independent variables. Serfling-type models are also used internationally, to identify the cyclical components in the time series using Fourier terms [20, 21]. As with the RMDM, no proxy for influenza activity is used. All the models mentioned use the same definition of excess values (observed minus expected number) but calculate the baseline differently. Regression models require a minimum sample size (unnecessary for the RMDM), and regression models' overall complexity is significantly increased and may be difficult for non-statisticians to apply.

Like the RKI model, our model is also subject to some limitations. Since we define excess as the difference between observed and expected values, we attribute every deviation from expected mortality/hospitalization within the influenza season to influenza. Other viruses that regularly circulate in addition to influenza, as well as other factors, might cause us to overestimate the excess in given weeks. An overlap with other virus epidemics, such as respiratory syncytial virus (RSV)—which also has a substantial impact in the winter season and could cause similar health results in some seasons—could not be ruled out. If possible, this should be controlled in a future model. Similarly, environmental temperature can have a substantial impact on mortality/hospitalization and should therefore be incorporated into predictive models to improve accuracy. Furthermore, smaller subgroups and weeks with fewer deaths on average might be more susceptible to random outliers. In very small groups, there is also always the possibility that excess—not revealed by the RKI model—could be random and not influenza-associated.

Analogous to the RKI method, we have set negative values to zero in the calculation of the excess. This a priori assumes that influenza can only increase the rate and does not decrease it. This can lead to a situation where positive random deviations are no longer neutralized by negative random deviations and the model thus produces an excess that does not exist in reality. With the awareness that we assumed a positive association between influenza and excess mortality/hospitalization, we wanted to maintain as many similarities to the RKI model as possible. So far, we have treated influenza by its presence alone (i.e., binary); other models incorporate the type of virus [14] or the strength of an influenza wave [16].

Like any other study based on secondary data, data collection was not adapted to our research questions. The information is limited to billable services and therefore influenced by coding quality of diagnoses and procedure; for example, diagnoses for patients are coded by healthcare providers that do not entirely correspond to the clinical picture of the patient.

CONCLUSION

This is the first study providing age-specific estimates of influenza-associated excess mortality and hospitalization in Germany. The results clearly show that the main burden of influenza is in the elderly, for whom prevention and treatment measures should be prioritized. Considering the fact that more than 95% of all influenza-associated deaths occur in the elderly, significant efforts should be made to increase vaccination coverage in this age group.

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Data Availability. The data that support the findings of this study, reference number (32, 33), are openly available from the RKI at https://influenza.rki.de/Saisonbericht.aspx; https://www.rki.de/DE/Content/Infekt/EpidBull/epid_bull_node.html. The data that support the findings of this study, reference number (29), are openly available from Destatis at https://www-genesis.destatis.de/genesis//online?operation=table&code=12411-0005&bypass=true&levelindex=0&levelid=1654004486617#abreadcrumb. The data that support the findings of this study, reference number (34, 35), are available from the FDZ. Restrictions apply to the availability of these data, which were used by Martin-Luther-Universität Halle-Wittenberg under license for this study. Data are available at https://doi.org/10.21242/23211.2018.00.00.1.1.0; https://doi.org/10.21242/23131.2017.00.02.1.1.0 with the permission of FDZ.

Declarations

Conflict of Interest. Christian J. A. Schindler and Tonio Schönfelder declare no conflicts of interest with respect to the research, authorship, and/or publication of this article; they are employees of WIG2 GmbH. Ian Wittenberg and Rafael Mikolajczyk declare no conflicts of interest with respect to the research, authorship, and/or publication of this article; Rafael Mikolajczyk is an employee of the Martin-Luther-Universität Halle-Wittenberg; Ian Wittenberg was an employee of the Martin-Luther-Universität Halle-Wittenberg at the time of the study and is now an employee of the Clinical Cancer Registry Saxony-Anhalt, Doctor-Eisenbart-Ring 2, 39120 Magdeburg, Germany. Oliver Damm and Rolf Kramer are employees of Sanofi-Aventis Deutschland GmbH.

Ethical Approval. No formal ethical approval was required as no primary collection of individual human data occurred, and only anonymized healthcare data were used. The used data from the RKI and Destatis are openly available, while the data from the FDZ required a permission. No patient consent was necessary as no primary collection of individual human data occurred and only anonymized healthcare data were used.

Permission to Reproduce Material from Other Sources. Apart from data mentioned in the data availability statement, no further third-party content was used, therefore permission was only needed for the FDZ. All quotations are provided with a reference.

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