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Investigating the impact of influenza on excess mortality in all ages in Italy during recent seasons (2013/14–2016/17 seasons)

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ABSTRACT

Objectives: In recent years, Italy has been registering peaks in death rates, particularly among the elderly during the winter season. Influenza epidemics have been indicated as one of the potential determinants of such an excess. The objective of our study was to estimate the influenza-attributable contribution to excess mortality during the influenza seasons from 2013/14 to 2016/17 in Italy.

Methods: We used the EuroMomo and the FluMomo methods to estimate the annual trend of influenza-attributable excess death rate by age group. Population data were provided by the National Institute of Statistics, data on influenza like illness and confirmed influenza cases were provided by the National Institutes of Health. As an indicator of weekly influenza activity (IA) we adopted the Goldstein index, which is the product of the percentage of patients seen with influenza-like illness (ILI) and percentage of influenza-positive specimens, in a given week.

Results: We estimated excess deaths of 7,027, 20,259, 15,801 and 24,981 attributable to influenza epidemics in the 2013/14, 2014/15, 2015/16 and 2016/17, respectively, using the Goldstein index. The average annual mortality excess rate per 100,000 ranged from 11.6 to 41.2 with most of the influenza-associated deaths per year registered among the elderly. However children less than 5 years old also reported a relevant influenza attributable excess death rate in the 2014/15 and 2016/17 seasons (1.05/100,000 and 1.54/100,000 respectively).

Conclusions: Over 68,000 deaths were attributable to influenza epidemics in the study period. The observed excess of deaths is not completely unexpected, given the high number of fragile very old subjects living in Italy. In conclusion, the unpredictability of the influenza virus continues to present a major challenge to health professionals and policy makers. Nonetheless, vaccination remains the most effective means for reducing the burden of influenza, and efforts to increase vaccine coverage and the introduction of new vaccine strategies (such as vaccinating healthy children) should be considered to reduce the influenza attributable excess mortality experienced in Italy and in Europe in the last seasons.

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Introduction

Seasonal influenza epidemics make a substantial contribution to the worldwide annual mortality rate, in particular among elderly individuals aged 65 years and over. Influenza associated deaths are highly variable by country and season (Iuliano et al., 2018). Factors

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influencing this variability may include the matching between circulating viruses and viruses included in the seasonal vaccine; environmental temperature; vaccination coverage and population demographics (e.g., the proportion of elderly individuals and/or of individuals with chronic conditions) (Vestergaard et al., 2017; Bonanni et al., 2015; Rizzo, 2015).

During the winter seasons 2014/15 and 2016/17, an excess of all-cause mortality was reported in Europe (Mølbak et al., 2015; Vestergaard et al., 2017). In both seasons, the predominant influenza virus strain circulating in Europe was A/H3N2, which is the strain most commonly associated with influenza mortality in the elderly (Vestergaard et al., 2017; ECDC/WHO, 2017; Rizzo et al., 2007). In Italy, the 2014/15 season was characterized by a co-circulation of A/H1N1pdm09 (52%) and A/H3N2 (41%) strains, while during the 2016/17 season, the A/H3N2 virus predominated (93%) (NIH, 2018).

In recent years, Italy has been registering peaks in death rates, particularly among the elderly during the winter season. A mortality rate of 10.7 per 1,000 inhabitants was observed in the winter season 2014/2015 (more than 375,000 deaths in absolute terms), corresponding to an estimated 54,000 excess deaths (+9.1%) as compared to 2014 (Signorelli and Odone, 2016), representing the highest reported mortality rate since the Second World War in Italy (UN, 2019). Although the above-described excess mortality created concern among researchers, health authorities and public health experts, it has been challenging to identify its determinants (Signorelli and Odone, 2016).

Excess mortality for influenza in Italy in the above mentioned seasons has been previously explored in a multi-country study (Vestergaard et al., 2017; Michelozzi et al., 2016; Cislaghi et al., 2016), analysing mortality data from a limited sample of the Italian population, and in a study focusing on a single Italian region (Fedeli et al., 2017).

The present study aims to investigate the two mortality peaks observed in Italy during 2015 and 2017, using the following data: a) census mortality data from all causes from 2013 to 2017; b) seasonal influenza like-illness surveillance data from 2013/14 to 2016/17 (week 42 to week 17); c) virological surveillance data from 2013/14 to 2016/17 (week 42 to week 17) and d) environmental temperature data for the same years. The final objective was to estimate the influenza-attributable deaths and the contribution of temperature variation to the excess mortality during the above mentioned influenza seasons, using a multiplicative Poisson regression model (EuroMOMO, 2018a).

Methods

Data sources

Deaths

Weekly number of deaths from all causes, by age group (0–4; 5–14; 15–64; 65–74; 75+), relative to the time period 2013–2017, were provided by the Italian National Institute of Statistics (ISTAT) (ISTAT, 2018a). Mortality data were available as weekly aggregated data from 2013 to 2016, and as monthly aggregated data for 2017. Therefore, for 2017, weekly deaths were estimated based on the proportion of weekly deaths, by age and sex, to the months averaged over previous years (2013–2016) in the same period.

Population

The number of deaths were reported, by week of death, as crude observed values and as direct standardized values, using the Italian resident population on 1/1/2014 as a reference. The size of the Italian population by age at the beginning of each year was obtained from ISTAT (ISTAT, 2019).

Influenza activity

Influenza-like illness (ILI) data were provided by the National sentinel influenza surveillance system (InfluNet), which has been in place in Italy since the 1999/2000 influenza season. InfluNet is a network of sentinel practitioners, representative of all Italian regions, based on the voluntary participation of an average 973 general practitioners and family pediatricians per year (range 754–1,055), providing health care to about 2% of the general population. InfluNet is dedicated to monitoring ILI incidence from week 42 to week 17 of each season, to defining the extent of the seasonal epidemics, and to collecting information on circulating strains (Perrotta et al., 2017; Gasparini et al., 2013).

Virological data were obtained from the InfluNet surveillance system. InfluNet is a virological surveillance system, in place since the 1999–2000 season, based on the collection throat swabs from a sample of the sentinel practitioners participating in InfluNet from week 47 to week 17 of each season (NIH, 2019). ILI and virological data were available by ISO week, and are reported weekly during the influenza season by the National Institutes of Health (NIH, 2019).

The sentinel surveillance system was planned to represent the Italian population by Region and by age group. The estimate of the total number of ILI cases in Italy were obtained by weekly ILI incidence, calculated on the population under surveillance, and re-proportioning these to the Italian population (about 60 million).

Environmental temperature

Italian temperature data were extracted from the National Oceanic and Atmospheric Administration (NOAA) database (NOAA, 2019). More than one hundred Italian weather stations contribute to the NOAA database, providing daily average, minimum and maximum temperatures. Overall, Italian daily average, minimum and maximum temperatures were obtained computing the means of daily average, minimum temperatures and maximum temperatures from each weather station, weighted by the populations of the Italian provinces where the stations were located for all of the study period (winter seasons from 2013/14 to 2016/17). Weekly average temperatures as well as weekly minimum and maximum temperatures were obtained calculating the weekly average of daily average, minimum and maximum temperatures. Based on these overall weekly temperatures, we estimated the expected weekly minimum and maximum temperature using a general linear model with a yearly seasonal variation applied to the data of the entire study period. Weeks with extreme temperatures (EC) were defined as weeks with an average temperature above the average of the maximum weekly temperatures or lower than the average of the minimum weekly temperatures. (Nielsen et al., 2018).

Statistical analysis

The number of influenza-attributable deaths was estimated using the FluMOMO algorithm, based on the weekly Influenza Activity (IA) and ET (EuroMOMO, 2018b). For this analysis, we used two IA indicators: 1) the ILI incidence and 2) the Goldstein index (ILI × percentage of positive specimens) (Goldstein et al., 2011). Up to two-weeks-delayed effects of the explanatory variables were considered in the model.

An explanatory factor reflecting the deviation of environmental temperature from the average maximum/minimum temperatures was introduced in the model in order to take into account a potential confounding effect of temperature on influenza excess mortality, as many Italian regions are affected by very cold weather in some winter weeks (e.g. January 2017). Very cold weather is recognized to have a potential impact on the excess mortality from all causes (Nielsen et al., 2011). Therefore, we estimated the influenza-attributable deaths among older adults, adjusting for

Extreme Temperatures (ET), defined as weeks with a mean temperature above the average maximum temperature or below the average. Periods with excess cold might be bad in the winter, but in summer, it may have a benign effect and opposite for periods with excess warmth. Therefore, the winter effect of temperature is included with an opposite warm (protective) and cold (harmful) effect.

The method has been described elsewhere (Vestergaard et al., 2017). In brief, we adopted a Poisson regression time-series model with over-dispersion, where the weekly absolute number of deaths from all causes was the outcome variable and IA and ET the explanatory variables. In the results section we reported results including both models with and without the ET effect. We corrected the model by annual trend, and seasonality. Seasonality was expressed as the sum of two sine waves of one year and half year periods, respectively (Nielsen et al., 2018). As the dominant type/subtype of influenza circulating viruses vary from season to season, a separate effect of IA for each season (season: week 42 to week 17 the following year) was used.

Analyses were performed separately for the age groups 0–4, 5–14, 15–64 and 65+ years of age, as well as for all ages. The statistical analysis was performed using STATA version 14 (StataCorp, 2014).

Results

National deaths

A total of 1,457,038 deaths were registered in Italy during the study period. Table 1 provides the absolute number of all-cause deaths, the overall crude mortality rate (per 1,000 inhabitants), the overall standardized mortality rate (per 1,000 inhabitants) and the standardized mortality rate by age group and by season. The number of deaths and the mortality rates from all causes increased by age. The 2014/15 and 2016/17 seasons showed the highest overall crude and standardized mortality rates.

Influenza-like illness and virological surveillance data

During the study period, an average of 5,290,000 (range 4,542,000–6,299,000) ILI cases were estimated in Italy, corresponding to a cumulative average incidence of 9% (range 8%–11%) in the Italian population. The highest estimated incidence was observed in children younger than 5 years (average of 23%, range 21%–26%) and in adolescents (average of 15%, range 12%–18%). The 2014/15 season showed the highest estimated number of cases, with a total of 6,300,000 ILI cases. The lowest number of cases was observed in the 2013/14 season, with 4,540,000 ILI estimated cases (Table 2).

A high circulation of A/H3N2 viruses was observed during all the seasons included in this study, although with a different proportion in each season. In two seasons (2014/15 and 2015/16), a co-circulation of A and B viruses was observed. In particular, during the 2014/15 season, the majority of circulating viruses were A (84%) with a co-circulation of A/H1N1pdm09 (52%) and A/H3N2 (41%). On the other hand, during the 2015/16 season, the majority were B (57%) viruses; among A viruses, the A/H3N2 subtype (56%) was the most frequently isolated, followed by the A/H1N1pdm09 (35%). In general, during all seasons there was a mismatch between the circulating viruses and the strains included in the vaccine (Table 3). The number of ILI cases and the number of positive and negative samples by week are displayed in Figure 1.

Influenza-attributable mortality

Figure 2 shows the weekly estimates of cumulative weekly mortality rates per 100,000 that can be attributed to the IA effect (with and without ET effect), over the winter seasons 2013/14 to 2016/17, derived from FluMOMO models. We observed two peaks, one for the 2014/15 and one for the 2016/17 season. These two seasons were also characterized by a high ILI incidence, particularly high for people aged 65 years and over (data not shown). The effect of temperature was marginal and more evident only in the 2016/17 season.

During the study period, 136,686 ILI-attributable excess deaths were estimated using the full model (IA + ET effect). The average annual mortality excess rate (MR) ranged from 40.6 to 70.2 per 100,000. The total number of excess ILI-attributable deaths during the 2014/15 season was 41,066, 65.6% higher compared to the previous season. During the 2016/17 season, the number of ILI-attributable excess deaths was 43,336, 57.9% more than the previous season.

Using the Goldstein index, the total number of excess deaths attributable to influenza in the 4-season study period was 68,068. The average annual mortality excess rate (MR) ranged from 11.6 to 41.2 per 100,000. Most of the influenza-associated deaths per year were among elderly individuals (≥65 years) (Table 3). During the 2014/15 and 2016/17 seasons, the influenza-attributable excess mortality was higher compared to 2013/14 and 2015/16. The total number of excess influenza-attributable deaths during the 2014/15 season was 20,259, three times as high compared to the previous season; and most of the influenza-attributable excess deaths were among individuals ≥65 years (96.1%, N = 19,475). A similar pattern was observed during the 2016/17 season, when the number of influenza-attributable excess deaths was 24,981, 58.1% higher compared to the 2015/16 season and 23.3% higher compared to the 2014/15 season.

Although most of the influenza-attributable excess deaths were reported among people aged ≥65 years, also the younger age classes showed a small increase. In particular, during the 2014/15 season, the influenza-attributable excess deaths, in the 0–4 and 15–64 age groups, were higher than the previous seasons. On the other hand, during the 2016/17 season, the influenza-attributable excess deaths were lower compared to the previous season in all age-groups, except for the 0–4 age group, in which the influenza-

Table 1

Number of all-cause cause-deaths and crude mortality rate (per 1,000 population) by age classes and winter season and standardized mortality rate (reference 2014 Italian population).

Age classes	2013/14		2014/15		2015/16		2016/17	
	N.	Rate	N.	Rate	N.	Rate	N.	Rate
0–4	942	0.35	923	0.34	848	0.33	948	0.36
5–14	255	0.04	223	0.04	224	0.04	254	0.04
15–64	38,548	0.99	39,773	1.01	38 070	0.97	39,05	1.00
65–74	48,958	7.62	50,563	7.77	48 129	7.37	51,357	7.86
75+	256,465	39.89	284,097	42.90	267 242	39.47	289,969	42.94
Total	345,168	5.72	375,579	6.18	354 513	5.84	381,578	6.28
Total std	345,168	5.72	366,507	6.08	340 226	5.64	366,859	6.08

Table 2
Number of estimated ILI cases and specific rate (per 1,000 population) by age classes and winter season and standardized mortality rate (reference 2014 Italian population).

Age classes	2013/14		2014/15		2015/16		2016/17	
	N.	Rate	N.	Rate	N.	Rate	N.	Rate
0–4	805,386	295.6	959,993	361.9	828,763	322.1	786,421	314.4
5–14	917,557	160.3	1,313,070	229.1	1,277,345	223.7	1,009,435	177.7
15–64	2,424,766	61,7	3,416,782	87.2	2,343,898	60.1	2,979,709	76.6
65+	394,292	30.3	609,156	46.1	426,994	31.9	664,436	49.1
Total	4,542,000	74.7	6,299,000	103.6	4,877,000	80.4	5,440,000	89.8
Total std	4,542,000	74.7	6,324,948	104.1	4,936,103	81.2	5,526,216	90.9

Table 3
Estimated cumulative influenza-attributable number of deaths and mortality rates (per 100,000) with confidence interval 95% (95% CI) in Italy in the winter seasons 2013/14–2016/17 using Goldstein Index as influenza activity.

Season	Proportion of circulating influenza viruses	Vaccine match with circulating viruses	0–4 years		5–14 years		15–64 years		Aged 65+		Total	
			N. 95% CI	Rate 95% CI	N. 95% CI	Rate 95% CI	N. 95% CI	Rate 95% CI	N. 95% CI	Rate 95% CI	N. 95% CI	Rate 95% CI
2013/14	A: 97% (H3: 58%; H1: 35%; Ans: 7%)	Good match	10	0.37	21	0.36	831	2.11	8460	65.01	7027	11.56
	B: 3% (Yamagata: 95%; Victoria: 3%)		3–20	0.1–0.7	11–32	0.2–0.5	406–963	1.8–2.4	7183–9803	55.2–75.3	5785–8347	9.5–13.7
2014/15	A: 84% (H3: 41%; H1: 52%; Ans: 7%)	A(H3N2) mismatch	28	1.05	5	0·08	1364	3.48	19475	147.32	20259	33.32
	B: 16% (Yamagata: 97%; Victoria: 3%)		19–39	0.7–1.5	3–8	0.0–0.1	1138–1602	2.9–4.1	16542–22567	125.1–170.7	18506–22064	30.4–36.3
2015/16	A: 43% (H3: 56%; H1: 35%; Ans: 9%)	A(H3N2) mismatch	0	0	15	0.27	977	2.5	10270	76.81	15801	26.05
	B: 57% (Yamagata: 5%; Victoria: 95%)		0–4	0.0–0.1	8–23	0.1–0.4	815–1148	2.1–2.9	8723–11900	65.2–89.0	14434–17293	23.8–28.4
2016/17	A: 95% (H3: 93%; H1: 1%; Ans: 6%)	Match with some aminoacidic substitution for the A(H3N2) component	38	1.54	13	0.23	675	1.74	19404	143.43	24981	41.23
	B 5% (Yamagata: 4%; Victoria: 96%)		26–53	1.0–2.1	7–20	0.1–0.4	563–793	1.4–2.0	17599–21267	130.1–157.7	23001–27014	38.0–44.6

H3 = A(H3N2); **H1** = A(H1N1)pdm09; **Ans** = A not subtyped.

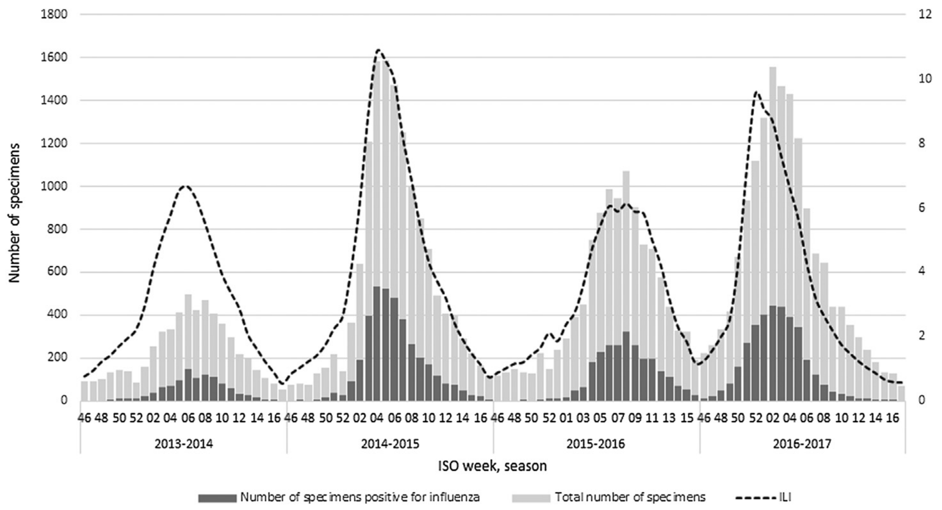

Figure 1. Total number of specimens, number of positive specimens for influenza and ILI cases (per 1,000 per inhabitants) by week and season. Italy, 2013/14, 2014/15, 2015/16 and 2016/17 season.

attributable excess deaths were the highest registered in the study period, as well as for the 65+ age group.

A comparison of the AI estimates using ILI and Goldstein index is reported in Table 4. The patterns were similar, but in 2014/15 and 2016/17 seasons the differences between ILI and Goldstein rates were larger, as well as for the age class 65+.

Temperature associated mortality

Extreme temperatures (either minimum or maximum) were recorded in 43% of the weeks (warm: 27%, cold: 16%), with a median extreme warm temperature of 0.7 (range: 0.1–2.3) degrees above the average weekly maximum temperature and extreme

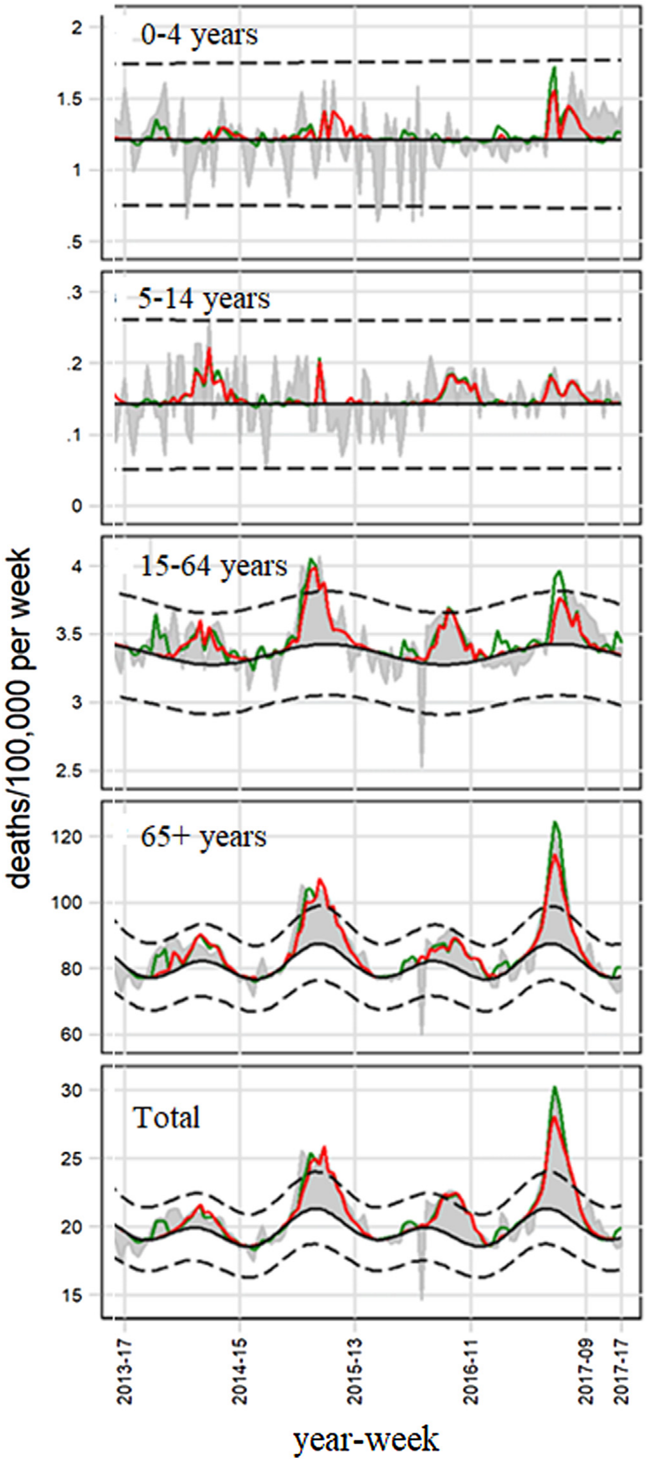

Figure 2. Excess mortality for winter seasons 2013/14, 2014/15, 2015/16 and 2016/17.
Note: Black line represents the baseline. Dotted line the 95% confidence interval. The shaded grey areas represent deviations in expected deaths from the estimated baseline. The red curves indicate mortality attributable to influenza activity, using the Goldstein index as the IA indicator, and the green curves indicate effect of IA + extreme temperatures.

cold: −0.7 (range: −0.3 to −2.6) degrees below the average weekly maximum temperature.

The overall number of deaths attributable to extreme ambient temperature in the study period was 8,820, ranging from 939 during winter 2014/15 to 5,190 during winter 2016/17, corresponding to a 3.6 average MR (range: 1.5 to 8.6, data not shown) per 100,000.

Discussion

With the present study we show a remarkable excess death attributable to influenza in Italy during the winter seasons 2014/15 and 2016/17, which was independent from mean weekly extreme temperature variations. Our results show that during these two seasons, in Italy, a high proportion of deaths was observed among the elderly (96.1% and 77.7%, respectively). However, high rates were also observed in children 0–4 years old (1.05 and 1.54/100,000, respectively).

The pattern of excess deaths attributable to influenza in Italy is comparable to the pattern observed in Europe, as obtained from the EuroMOMO network (Nielsen et al., 2018). The EuroMOMO network reported, in 2014/15 and 2016/17 seasons, a higher excess death for all causes, in all ages, compared to the previous season: 28.58/100,000 in 2014/15 and 25.65/100,000 in 2016/17. In the same seasons, the highest all-cause excess mortality was reported among people aged 65+. According to previous studies conducted at the European level, all-cause mortality is mainly attributable to seasonal variations in IA (Nielsen et al., 2018).

We estimated influenza-associated mortality using two indicators of influenza activity. When using ILI as the IA, mortality may be overestimated. By using the Goldstein index as the IA, the dynamic of transmission is better represented and overestimation due to deaths by other pathogens is limited (Nielsen et al., 2018). Both indicators show a similar pattern, but the estimation of mortality associated with influenza based on the Goldstein index seems to be the most reliable. We considered ILI as IA indicator mainly for comparisons with previous studies adopting the same approach.

In 2014/15, among people aged 65+, European pooled data (EuroMOMO Network, 2015) showed an increased influenza-attributable mortality rate of 147.41/100,000 deaths, with ILI as IA indicator. Using the same model for Italy, we estimated a rate of 292.8/100,000 (CI 95% 279.7–306.0/100,000), perfectly comparable with the rate reported at the EU level. The 2014/15 season in Europe was, as in Italy, characterized by co-circulation of influenza A/H3N2 and influenza A/H1N1pdm09 viruses, but the A/H3N2 virus strain was more commonly detected compared to season 2013/14 (Mølbak et al., 2015).

A similar pattern was reported in the elderly in EU during the 2016/17 season, with an excess influenza-attributable mortality rate of 129.9/100,000 deaths (Vestergaard et al., 2017) Italian estimates (using the Goldstein index) showed a rate of 143.43/100,000 (CI 95% 130.09–152.72), slightly higher compared to the European rate.

Scarce data is available on influenza-attributable mortality estimates for single countries in the study period considered. However, some studies have been published that have reported influenza-attributable excess mortality rates in EU countries. In particular, Italy shows a higher influenza attributable excess mortality compared to Denmark in all ages, with highest levels reported in elderly, but for the 0–4 age group where Denmark reported higher rates compared to Italy in all seasons, except for the 2014/2015 season (0.52/100,000 vs 1.05/100,000) (Nielsen et al., 2018). In Sweden, the 2016/17 season was characterized by the predominant circulation of A/H3N2. In this season, the reported influenza-attributable mortality in the elderly was higher compared to other age groups, and was the highest recorded, compared to previous A(H3N2) dominated seasons (Public Health Agency of Sweden, 2017). In the UK, estimates of the annual number of deaths directly attributable to influenza range from 4 to

Table 4
Comparisons between the different influenza activity indicators: influenza-associated mortality rates (per 100,000) estimates based on Goldstein Index and Influenza Like Illness, by age group and winter season.

Season	0–4 years		5–14 years		15–64 years		Aged 65+		Total	
	N. 95% CI	Rate 95% CI	N. 95% CI	Rate 95% CI	N. 95% CI	Rate 95% CI	N. 95% CI	Rate 95% CI	N. 95% CI	Rate 95% CI
Influenza Like Illness										
2013/14	3	0.1	27	0.48	698	1.78	24063	184.89	24791	40.61
	0–9	0.0–0.3	18–38	0.5–1.1	540–871	1.4–2.2	22617–25538	173.8–196.2	23333–26283	38.2–43.1
2014/15	24	0.89	5	0.98	2337	5.96	38700	292.76	41066	67.13
	14–35	0.5–1.1	3–6	0.6– 1.2	2194 – 2483	5.6–6.3	36971–40455	279.7–306.0	39184–42978	64.1–70.3
2015/16	11	0.41	19	0.34	1043	2.67	26390	197.39	27463	45.02
	4–19	0.1–0.7	12 – 28	0.2–0.5	809–1309	2.1–3.3	24963–27843	186.7–208.2	26022–28933	42.7–47.4
2016/17	34	3.35	20	0.36	2029	5.22	41223	304.78	43366	70.19
	67–102	2.7–4.1	13 – 29	0.2–0.5	1888 – 2173	4.9–5.6	24963–27843	290.4–319.4	41258–45511	66.8–73.7
Goldstein Index										
2013/14	10	0.37	21	0.36	831	2.11	8460	65.01	7027	11.56
	3–20	0.1–0.7	11–32	0.2–0.5	406–963	1.8–2.4	7183–9803	55.2–75.3	5785–8347	9.5–13.7
2014/15	28	1.05	5	0·08	1364	3.48	19475	147.32	20259	33.32
	19–39	0.7–1.5	3 –8	0.0–0.1	1138–1602	2.9–4.1	16542–22567	125.1–170.7	18506–22064	30.4–36.3
2015/16	0	0	15	0.27	977	2.5	10270	76.81	15801	26.05
	0–4	0.0– 0.1	8–23	0.1–0.4	815–1148	2.1– 2.9	8723–11900	65.2–89.0	14434–17293	23.8–28.4
2016/17	38	1.54	13	0.23	675	1.74	19404	143.43	24981	41.23
	26–53	1.0–2.1	7–20	0.1– 0.4	563–793	1.4–2.0	17599–21267	130.1–157.7	23001–27014	38.0–44.6

14,000 per year, with an average of around 8,000 per year (Public Health England, 2014). Moreover, influenza-attributable excess deaths using the FluMomo method for UK were reported in 2014/15 (Pebody et al., 2018). UK estimates, in terms of absolute numbers, were higher compared to Italian data, in all ages and in particular in the elderly (26,542 vs 19,475 respectively).

Plausible hypotheses regarding the determinants of the observed excess deaths attributable to influenza in Italy, especially in the old population (i.e. 65+), are: i) meteorological factors (low and high temperatures), ii) seasonal influenza circulating virus strains, and iii) the amplitude of the at risk population (pools of elderly).

Deviation from expected temperature may have a great impact on mortality (Allen and Sheridan, 2018). Very low temperatures were registered at the beginning of 2017 in various European countries. Therefore, we decided to adjust our estimates of influenza-associated mortality for extreme temperatures. We found that the impact of extreme temperatures on mortality in Italy was quite limited, with the exception of the 2016/17 season. Despite this impact of extreme low temperatures, most of the excess death rate registered in 2016/17 is attributable to influenza, confirming other observations recorded in Europe (Nielsen et al., 2019). Nevertheless, this is the first study reporting the effect of temperatures on mortality in Italy, and we acknowledge that this association has to be further investigated, also analyzing this factor at sub-national level.

As in other European countries, the excess mortality observed in Italy during the 2014/15 and 2016/17 seasons could be related to the circulation of an A/H3N2 influenza virus, which is known to be associated to a higher mortality in the elderly (Nielsen et al., 2019). The A/H3N2 strain was strikingly prevalent in 2016/17 compared to previous seasons, with a mismatch between the circulating A/H3N2 virus and the virus included in the vaccine composition, which may have caused a low vaccine effectiveness (Rizzo et al., 2016). This is confirmed by case control studies conducted in the elderly population at the EU level (Kissling et al., 2016; Valenciano et al., 2016), showing moderate to low influenza vaccine effectiveness estimates both in primary care and in hospital settings, especially for the A/H3N2 component of the vaccine.

The vaccine coverage in the elderly in both seasons was close to 50% (Bonanni et al., 2018). In Italy, annual influenza vaccination is targeted to persons aged 65 years or above and for high risk persons aged more than 6 months (including pregnant women, individuals with chronic conditions, etc.). In the last 10 years the influenza vaccine coverage progressively declined until 2015, especially in those aged 65+ (68% in 2005/06 to 49% in 2014/15 season), which is well below the WHO minimum target (75%) (Ministry of Health, 2018). One study, reporting an excess of mortality in 2015 in the Italian city of Bologna, showed that elderly individuals unvaccinated against influenza had an increased risk of all-cause and cause-specific mortality compared to vaccinated individuals (Francia et al., 2018).

In terms of amplitude of the at risk population, in Italy there are 6.7 million of people aged 75+ (more than 10% of the population) that constitute a large group of fragile subjects, among which the annual death rate is naturally high, around 4% (ISTAT, 2018b). Among them, a large variation in the absolute number of deaths causes small fluctuations in the mortality rate. Excess deaths constitute a serious public health issue that can be prevented coupling influenza vaccination with personal protection measures (ECDC, 2019).

This study has several limitations. The influenza surveillance system in Italy is based on voluntary general practitioners reporting ILI cases, and the participating general practitioners are not selected with random criteria. Another important limitation in the surveillance system is related to virological surveillance because sampling of influenza testing may be biased towards more samples taken at hospitals, and therefore may overestimate the proportion of positive samples in the population. These limitations may introduce a potential bias due to the selection of subjects under surveillance.

Moreover, the study is based on census mortality data, while previous published studies (Nielsen et al., 2019) were based on sample data and limited to regional data. However, the proposed model uses all-cause weekly mortality data, usually available quite in real time in many countries, and can therefore be a valuable tool for monitoring the seasonal impact of influenza.

The study should be validated using cause specific mortality data, which, however, was not available for the entire study period. Furthermore, it would be valuable to investigate also regional patterns, but such details on mortality were not available in the study period considered.

To evaluate whether the association of influenza activity with mortality varied with temperatures, an interaction term of influenza activity and temperatures should be added to model. The adopted statistical model did not include an interaction term between temperatures and IA. This "rigidity" of the model can be considered a limitation and should be overcome in future applications.

Finally, the pattern of the effect of temperature on mortality should be investigated further to be able to obtain more valid estimated of the impact of this effect, e.g. testing different cut-off values for the extreme temperature definition.

Assessment of winter mortality in Italy, during the 2014/15 and 2016/17 seasons, confirmed the hypothesis that influenza was likely to have been the main contributor to the excess mortality seen, especially in the elderly. Routine use of methods, such as FluMoMo can assist in rapidly assessing the impact of influenza in the overall mortality, which varies considerably by age group and type of circulating viruses. In conclusion, the unpredictability of the influenza virus circulating strains continues to present a major challenge to health professionals and policy makers. Nonetheless, vaccination remains the most effective means for reducing the burden of influenza, with a particular impact on the influenza attributable mortality. Moreover, the influenza vaccine, by reducing influenza complications, can indirectly reduce morbidity and mortality from all causes in the elderly (Trucchi et al., 2015). An improved protective effect on the elderly population could be obtained also by reducing the circulation of the influenza viruses through vaccination strategies targeting healthy children, who represent a crucial reservoir of the virus (Pebody et al., 2015; Grijalva et al., 2010; King et al., 2005; King et al., 2010).

Contributors

AR projected and designed the study, analysed the data, and participated in drafting the paper. AB contributed in manuscript writing and analysed the ILI InfluNet data. AA and FG contributed in preparing tables, manuscript writing, and editing. PP reviewed critically preliminary results and commented on manuscript. SM provided the data on mortality and reviewed the statistical section. WR supervised the study and contributed in the discussion. CR conceived the study, drafted and edited the manuscript.

Declaration of interest

All the authors have no conflict of interest to declare.

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Ethical approval

No ethical approval is requested.

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