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All-cause mortality during the influenza season 2019-2020: comparison with previous influenza seasons in the territory of the local health authority "Central Tuscany", Italy

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Key words: Influenza season, excess mortality, COVID-19
Parole chiave: Stagione influenzale, eccesso di mortalità, COVID-19

Abstract

Introduction. *Because of the 24 months latency in the release of official data on causes of death, and in consideration of the limited testing capacity during the first pandemic wave, to estimate the COVID-19-related mortality in 2020, the evaluation of all-cause mortality excess is often used instead. Our study aimed at assessing whether in Central Tuscany, Italy, an excess all-cause mortality occurred in the 2019-2020 influenza season, which partly overlapped with the months of the first pandemic wave in which the impact of COVID-19 was the highest.*

Materials and Methods. *Age- and sex-adjusted mortality rates for 2019-2020 influenza season were compared with those of influenza seasons 2009-2010 to 2016-2017.*

Results. *No all-cause mortality excess was observed in the 2019-2020 influenza season, which, on the contrary, was characterized by the lowest all-cause mortality rate.*

Conclusion. *Our finding can be explained by the imposition, in early March 2020, of a national lockdown, which came into effect in an early epidemic phase in Tuscany, and thus limited the transmission of SARS-CoV-2 infection, as well as influenza, in the territory. In March and April, by causing the death of vulnerable elderly patients who had been spared by the mild seasonal flu in the prior months, COVID-19 acted with a harvesting effect.*

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Introduction

Each year excess deaths from all-cause are observed during influenza season. This phenomenon disproportionately affects the elderly and those at high cardiovascular risk (1), and is mainly driven by influenza virus, but also by other viral or bacterial respiratory infections that, like influenza, are more common in the fall and winter, as well as by the impact of cold snaps on cardiovascular diseases, especially in countries with milder climates (2, 3). It varies between years, and it depends also on the intensity of influenza transmission, on the influenza vaccination coverage reached each year and on the level of correspondence between circulating and vaccine influenza subtypes and lineages. In addition, the short-term effects of atmospheric pollution need to be mentioned, even if the burden of disease due to atmospheric pollution in the Central Tuscany area is not as high as in other areas of Italy (e.g., the Po Valley). In fact, day-to-day changes in air pollutants are significantly associated with excess mortality even at levels below currents air quality standards (4). Air pollution increases the risk of both "natural" death and of death from cardiovascular and respiratory diseases (5).

The COVID-19 epidemic broke out in Italy at the end of February 2020, while influenza was still active, and caused a total of over 45,000 deaths by the end of April, determining a substantial excess total mortality, about 60% greater than the number of officially registered COVID-19 deaths, due to under-registration of COVID-19 deaths in that period (6). The true burden of COVID-19 in terms of deaths was heavily underestimated due to poor testing capacity, as often deaths occurred in patients before they could be tested for SARS-CoV-2 infection (7). Because of underestimation of COVID-19 deaths in the first pandemic wave, and considering the 24 months delay in the release of official data on causes of death by the Italian National Institute of Statistics, one way to estimate COVID-19-related mortality in the first pandemic wave is to evaluate the excess all-cause mortality instead (6, 7).

During the first pandemic wave, SARS-CoV-2 infections distribution in Italy was more limited in Central and Southern regions than in the Northern ones, e.g., Lombardy and Veneto (8). Our study aimed at evaluating whether in the territory of the Central Tuscany Health Authority (CTHA), Italy, an excess all-cause mortality occurred during the 2019-202 influenza season, which partly overlapped with the months of the first pandemic wave, March and April 2020, in which the impact of COVID-19 was the highest.

Materials and Methods

The data source for deaths from all causes that occurred during the 2019-2020 influenza season is represented by the *Anagrafe Nazionale delle Posizioni Residenziali* (ANPR), which regularly and promptly collects demographic information regarding residents of municipalities and is validated by the Italian Ministry of the Interior, whereas for those occurred from 2009 to 2017 data from the Regional Mortality Register of Tuscany were used. As of February 2021, the Regional Mortality Register is updated up to the year 2017.

Person-years of exposures for the periods corresponding to influenza season were calculated. For analyses of all-cause mortality, five-year age groups up to 84 years (<5; 5-9; 10-14; ... 80-84) were considered, whereas the last age group comprised all those ≥85 years. Sex- and age-adjusted mortality rates in a 28 week-period starting the 42nd week of 2019 and ending the 17th week of 2020, were compared with those observed in corresponding periods since

2009-2010 to 2016-2017. These weeks of observation, from mid-October to the end of April of the following year, are those in which epidemiological and virological surveillance for seasonal influenza is in place. Due to the lack of mortality data for 2017-2018 and 2018-2019 influenza seasons were not taken into account.

Direct standardization in each influenza season was used to calculate sex and age-standardized mortality rates observed in the CTHA territory, which comprises the provinces of Florence, Prato, Pistoia and 4 municipalities of the province of Pisa, and covers over 1,6 million residents. The age distribution of the person-years at risk in flu season 2019-2020 was used as the standard population. We also computed direct standardized rates for residents >64 years.

Finally, indirect standardization was applied to estimate the standardized mortality ratios (SMRs) for 2019-2020 season. SMR is the ratio between the observed number of deaths in flu season 2019-2020 and the number of deaths that would be expected, based on the age and sex-specific mortality rates of the previous eight flu seasons considered. Expected deaths in 2019-2020 season were calculated according to the formula:

$$\text{N Expected Deaths} = \Sigma(\text{Standard age- and sex-specific death rate}) \times (\text{Study age- and sex-specific population})$$

where the Standard age and sex-specific death rate is the overall age and sex-specific mortality rates of all prior seasons, and the Study age and sex-specific population is represented by the age and sex-specific person-years at risk in 2019-2020 season.

All-cause mortality rates and SMRs with 95% confidence intervals (95% CI) were generated using STATA software, version 15 (STATA Corp, College Station, TX).

Results

During the nine considered influenza seasons, there were four seasons with high all-cause mortality, i.e., with standardized rates above 1,300 per 100,000 population; these were 2009-2010 (the year of H1N1 pandemic); 2011-2012; 2014-2015 and 2016-2017 (Table 1). Three influenza seasons were characterized by intermediate all-cause mortality rates, between 1,200 and 1,300 per 100,000 (2010-2011; 2012-2013; 2013-2014), and the remaining two, 2015-2016 and 2019-2020, were low-impact seasons with mortality rates < 1,200 per 100,000.

Conversely, the standardized mortality rates in the months of each year not included in such periods of observation, e.g., from week 18 to week 41 of each year, were always lower than 1,100 per 100,000 except for the year 2012, in which a 1,197 per 100.000 all-cause mortality rate was observed.

In the 2019-2020 flu season, 10,151 deaths occurred, compared to 11,111 expected on the basis of the age and sex-specific mortality rates from flu season starting from 2009-2010 to flu season 2016-2017, the SMR being significantly lower, 0.91 with 95% CI 0.90-0.93. Stratifying by gender, SMRs were significantly lower both in males (0.89, 95% CI 0.87-0.92) and females (0.93, 95% CI 0.90-0.95).

Mortality rates in influenza season were much higher in individuals aged 65 years or older (Table 2). However, even when considering this age group, no all-cause mortality excess was observed in 2019-2020 influenza season compared with previous seasons. Seasons characterized by the highest rates were 2016-2017, 2011-2012 and 2009-2010, whereas 2019-2020 was the second with the lowest mortality rate after 2013-2014 influenza season. In the 2019-2020 flu season, 9,283 deaths occurred in residents ≥64 years, compared

Table 1 - Number of deaths from all causes in the general population, person-years of observation, crude and sex- and age-adjusted all-cause mortality rates per 100,000 with 95% confidence interval (CI) in 2009-2010 to 2016-2017 influenza seasons and in 2019-2020 in central Tuscany Local Health Authority (standard ISTAT population 2020).

	No of deaths	No of person-years	Crude rate per 100,000	Adj. rate per 100,000 (95% CI)
2009-2010	9,586	854,325	1,122.1	1,340.0 (1,314.4-1,365.6)
2010-2011	9,450	860,615	1,098.1	1,292.8 (1,267.9-1,317.6)
2011-2012	10,085	865,821	1,164.8	1,349.3 (1,324.3-1,374.3)
2012-2013	9,625	845,842	1,137.9	1,278.7 (1,254.3- 1,303.0)
2013-2014	9,697	855,761	1,133.1	1,254.7 (1,230.9-1,278.5)
2014-2015	10,457	872,022	1,199.2	1,316.9 (1,293.0 -1,340.8)
2015-2016	9,604	874,926	1,097.7	1,181.4 (1,158.8. 1,204.0)
2016-2017	11,123	875,276	1,270.8	1,349.3 (1,325.6- 1,373.0)
2019-2020	10,151	876,957	1,157.5	1,177.8 (1,156.0- 1,199.7)

to 10,134 expected on the basis of the age and sex-specific mortality rates during the flu seasons 2009-2010 to 2016-2017, the SMR being significantly lower, 0.92 with 95% CI 0.90-0.93. Stratifying by gender, SMRs were significantly lower both in males (0.89, 95% CI 0.87-0.92) and females (0.93, 95% CI 0.90-0.95).

Discussion and conclusions

In Central Tuscany, no all-cause mortality excess in the 2019-2020 influenza season was observed, despite the period partially overlapped with the first wave of COVID-19 epidemic in Italy. On the contrary, deaths in older adults and in the general population were significantly lower than the average number of deaths occurred in 2009-2010 to 2016-2017 influenza seasons. We believe that this finding can be at least partially explained by the so-called *harvesting* effect, i.e., the death in March and April for COVID-19 of old or very old people, affected by serious chronic conditions and who had been spared by seasonal flu in prior months. From ISTAT data on all-cause mortality by municipalities (9), we calculated, in the territory of Central Tuscany Health Authority, a 21% of excess

Table 2 - Number of deaths from all causes in residents over 64 y, person-years of observation, crude and sex- and age-adjusted all-cause mortality rates per 100,000 with 95% confidence interval (CI) in 2009-2010 to 2016-2017 influenza seasons and in 2019-2020 in central Tuscany Local Health Authority.

	N of deaths	N of person-years	Crude rate per 100,000	Adj. rate per 100,000 (95% CI)
2009-2010	8,622	195,029	4,420.9	4,912.9 (4,814.6-5,011.2)
2010-2011	8,473	196,044	4,322.0	4,721.4 (4,626.0 – 4,816.7)
2011-2012	9,152	197,471	4,634.6	4,973.5 (4,877.2- 5,069.8)
2012-2013	8,649	198,259	4,362.5	4,655.1 (4,562.0- 4,748.2)
2013-2014	8,798	203,347	4,326.6	4,600.5 (4,509.2-4,691.8)
2014-2015	9,538	208,269	4,579.7	4,846.5 (4,754.8-4,938.2)
2015-2016	8,743	211,314	4,137.4	4,331.0 (4,244.7- 4,417.4)
2016-2017	10,225	212,696	4,807.3	4,992.8 (4,901.5-5,083.9)
2019-2020	9,283	216,158	4,294.5	4,331.6 (4,248.0-4,415.2)

deaths in March and April 2020 compared to the average number of deaths in the corresponding months from 2015 to 2019. On the contrary, in January and February 2020 there were 9.5% fewer deaths than in the same period from 2015 to 2019. As a matter of fact, the 2019-2020 flu season had an intermediate intensity, and air temperatures reached that winter were particularly mild and very few cold snaps occurred. The progression of 2019-2020 seasonal influenza showed a trend common to most flu seasons, with the intensification of viral activity at the start of the year and the peak was reached between the end of January and the beginning of February 2020 (8). Contrary to what happened in other Italian regions, in Tuscany the influenza intensity at the peak reached in the fifth week of 2020 was not high, but medium, with an estimated 8.4 cases per 1,000 population. It is estimated that less than 400,000 Tuscany residents got sick with flu, whereas e.g., the number estimated for the 2018-2019 was 520,000 (10).

In addition, on March 9th, 2020, a national lockdown was imposed on account of the acceleration of the COVID-19 outbreak in the Northern regions of Italy, in which the disease had already hit the population with dramatic intensity. Lockdown measures included travel restrictions, closure of all non-essential businesses and industries and stay-at-home orders, and came into effect in Tuscany in an earlier epidemic phase, thus limiting the transmission of SARS-CoV-2 infection, as well as influenza, in the territory.

Influenza vaccination in Italy is actively offered each year to priority groups, such as all individuals over 64 years of age, those institutionalized in residential or long-term facilities, subjects aged from 6 months to 64 years suffering from chronic diseases, pregnant women, family members and contacts of patients at risk of complications and healthcare workers. As for the influenza vaccination coverage, in Tuscany in the ≥65 years population it has been quite stable in the last four years on values around 55-56%, somewhat higher than the national average (for the 2019-2020 influenza season, 56.4% versus 54.6%). Vaccination uptake is higher than the average national value also in the general population (20.1% versus 16.8%).

All these factors contributed to generate all-cause mortality rates in line with those expected on the basis of trends from previous influenza seasons and highlight the fact that if SARS-CoV-2 was already present in the territory earlier than February 2020, when the regional COVID-19 surveillance system first detected its presence, as some evidence suggested (11), its circulation was still not widespread.

Riassunto

Mortalità per tutte le cause durante la stagione influenzale: confronto tra la stagione 2019-2020 e quelle precedenti nel territorio dell'Azienda USL Toscana Centro

Introduzione. L'unica fonte informativa ufficiale per l'analisi delle cause di morte è rappresentata dalla scheda ISTAT di decesso. Tuttavia, ISTAT rende disponibili i dati riportati sulla scheda di decesso con una latenza di 24 mesi, tempistica accettabile in una situazione di normalità, ma non sufficientemente tempestiva in situazioni epidemiche come quella attuale. Inoltre, data la limitata capacità di effettuare test diagnostici durante la prima ondata pandemica, i decessi per COVID-19 nella prima parte del 2020 rischiano di essere sottostimati. Pertanto la stima dell'eccesso di mortalità complessiva (non per causa) è sovente utilizzata come *proxy* dell'eccesso di mortalità correlato a COVID-19 nel 2020. L'obiettivo del nostro studio è stato quello di valutare se nel territorio dell'Azienda USL Toscana Centro, che comprende le province di Firenze, Prato e Pistoia e quattro comuni in provincia di Pisa, si sia verificato un eccesso di mortalità per tutte le cause nella stagione 2019-2020, che si è in parte sovrapposta ai mesi della prima ondata pandemica da SARS-CoV-2 in cui l'impatto di COVID-19 è stato più elevato, rispetto alle precedenti stagioni influenzali.

Materiali e metodi. I tassi di mortalità aggiustati per età e sesso per la stagione influenzale 2019-2020 sono stati confrontati con quelli delle stagioni dal 2009-2010 al 2016-2017.

Risultati. Nessun eccesso di mortalità per tutte le cause è stato osservato nella stagione influenzale 2019-2020, che, al contrario, è stata la stagione caratterizzata dal tasso di mortalità più basso.

Conclusione. Il lockdown generalizzato, entrato in vigore nel nostro territorio quando l'epidemia da SARS-CoV-2 era ancora in una fase inziale, ha limitato la trasmissione dell'infezione. Gran parte dell'eccesso di mortalità osservato tra marzo e aprile è dovuto all'effetto *harvesting* da parte di COVID-19, che ha causato il decesso di persone perlopiù anziane e/o con seri problemi di salute preesistenti che erano sopravvissute a un inverno mite e ad una stagione influenzale di intermedia intensità.

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