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Influenza-related mortality in the Italian elderly: No decline associated with increasing vaccination coverage

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Abstract

We investigated trends in influenza-related mortality among the elderly population in Italy associated with increased vaccination coverage. Using Italian vital statistics data, we studied monthly death rates for pneumonia and influenza and all-cause for persons ≥65 years of age by 5-year age groups for 1970–2001. Using a classic seasonal regression modelling approach, we estimated the age-specific seasonal excess mortality rates among Italian elderly as a measure of influenza-related deaths. We studied trends in excess mortality after adjusting for population aging and analyzing separately seasons dominated by the severe A/H3N2 subtype and those dominated by other circulating influenza subtypes. After the late 1980s, no decline in age-adjusted excess mortality was associated with increasing influenza vaccination distribution primarily targeted for the elderly. These findings suggest that either the vaccine failed to protect the elderly against mortality (possibly due to immune senescence), and/or the vaccination efforts did not adequately target the frailest elderly. As in the US, our study challenges current strategies to best protect the elderly against mortality, warranting the need for better controlled trials with alternative vaccination strategies.

Keywords: Influenza; Vaccination; Mortality

1. Introduction

The incidence of severe outcomes of influenza increases substantially with age and for individuals with high-risk conditions [1,2]. During seasonal epidemics persons aged 65 years and older account for more than 90% of all influenza-related deaths with an exponential increase in death rates for each decades past 65 years [3,4].

Influenza diagnoses are generally not laboratory confirmed, and deaths related to influenza are often attributed to co-morbid conditions or to secondary complications that occur after the influenza virus infection [5]. For these reasons, influenza-related mortality is traditionally quantified indirectly using statistical methods that estimate the seasonal increases in pneumonia and influenza (P&I) or all-cause (AC) mortality above a baseline of expected mortality, which occurs concurrently with influenza virus circulation [6–11]. Since the 1968 influenza A(H3N2) Hong Kong pandemic, the seasonal influenza-related mortality burden has fluctuated widely, depending on which one of the circulating virus subtypes (influenza A(H3N2), A(H1N1) and B) dominate. The highest mortality rates typically occur in seasons dominated by A(H3N2) viruses [12].

During the last three decades, the life expectancy and the proportion of elderly in the Italian population has increased more than in other European countries In particular, the population size of elderly >85 years of age has doubled from 1990

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to 2001 [13]. With this ageing of the population one might expect an increase in influenza related mortality, due to the exponential risk of influenza-related death with age among elderly [3,4]. In Italy, since 1980 influenza vaccination has been recommended for people 65 years of age and older, those with chronic diseases (respiratory, cardiovascular, renal conditions), children under 12 years of age who are receiving long-term anti-inflammatory treatment with aspirin, and those who have frequent contact with these high risk groups and may transmit influenza to them [14]. Vaccination coverage among the elderly population in Italy increased slowly from 1980 to 1987, then rose sharply to ∼60% from 1988 to 2001 [15,16] (Table 1).

There is considerable discrepancy in measurements of influenza vaccine benefits in observational cohort studies and national trend studies. A large body of observational cohort studies comparing mortality in vaccinated and non-vaccinated elderly have consistently reported a 50% reduction in all winter deaths in vaccinated elderly [17,18]. However, such cohort studies are prone to self-selection bias that may lead to substantial overestimation of mortality benefits. Recent cohort studies set in the UK [19] and the US [20] found similar reductions in all-cause mortality between vaccinated and unvaccinated elderly outside influenza epidemic periods, indicating a vaccination receipt bias rather than protection from influenza-related mortality. It was also found that adjustment procedures using broad disease classification codes and typically used for cohort studies were not adequate [21]. Moreover, a recent study of long-term trends in influenza-related mortality among US elderly reported a lack of mortality benefits associated with the vaccination efforts [12]. The lack of observed vaccine mortality benefits in the elderly at the population level is further supported by a recent review of influenza vaccine immunogenicity, demonstrating that the antibody response in the elderly was considerably lower than that of younger adults [22].

To evaluate the mortality benefits that may be attributed to the increasing vaccination coverage in the Italian elderly and confirm or infirm the results of the US trend study [12], we investigate trends in influenza-related excess mortality in Italy, adjusting for population aging and changes in virus subtype circulation. For comparison purposes, we use a methodological approach very similar to the US study [12].

2. Methods

2.1. Mortality and population data

The monthly numbers of pneumonia and influenza (P&I) and all-cause (AC) deaths in Italy were obtained from death certificates collected by the Italian National Census Bureau (ISTAT) from 1970 through 2001. We identified P&I deaths from underlying cause of death statistics from the International Classification of Diseases (ICD), codes 480–486 and 470–474 from ICD-8th (1970–1979) and 480–486 and 487 from ICD-9th revisions (1979–2001).

For each year, we generated summary data sets of the monthly numbers of influenza, P&I and AC deaths, stratified by 5-year age intervals (65–69, 70–74, 75–79 and 80–84), and for ≥85 years old. As a non-historic control, we also studied mortality trends in a younger age group 45–64 years, an age group associated with a very low vaccination coverage (∼6% in 1999–2001).

We obtained annual population estimates from the Italian National Census Bureau from 1970 to 2001, and calculated the annual number of elderly in each age group. We then calculated monthly mortality rates per 100,000 for each age group, and standardized these to 30.4-day months.

2.2. Influenza vaccination coverage in people over 65 years

From 1980 to 1999 our estimates of vaccine coverage were based on data on vaccine distribution and use collected routinely by the Ministry of Health (personal communication: Dr. Dina De Stefano Caraffa) from the local health departments and general practitioners who administer vaccines to the population. These data represented the total number of vaccine doses distributed, and provide an indirect measure of vaccination coverage. Although the data is not specific by age group, we assumed a proportionate distribution of vaccine based on the proportion of the total population groups for whom vaccine is recommended. In Italy, influenza vaccination is recommended [14] for those over 65 years of age, younger persons with chronic conditions, and children under 12 years of age on long-term aspirin therapy, the latter two representing 8% of the total population [13]. Therefore, we estimated that the overall number of doses distributed in Italy from 1980–1999 was a good proxy for the number of doses distributed in the elderly population.

For more recent years, 1999–2001, age-specific influenza vaccine coverage was estimated from the distribution rates in non-institutionalized elderly ≥65 years of age [23].

2.3. Virological surveillance

For each influenza season from 1970 to 1980, we reviewed annual Weekly Epidemiological Report listing influenza viral subtypes identified in Italian laboratories during each influenza season [24]. For seasons from 1980 to 2001, we obtained the proportion of each circulating influenza subtype (A(H3N2), A(H1N1), and B), using laboratory surveillance data from the Italian National Influenza Centre of the WHO ([25,26] and Dr. Donatelli, personal communication).

We considered an influenza subtype to be dominant when it accounted for at least 50% of all isolates that were subtyped in that season. Of the 31 seasons studied, A(H3N2) viruses predominated in 20, the remaining 11 seasons were dominated by A(H1N1) or influenza B viruses (Table 1).

Table 1
Dominant influenza virus subtype, influenza vaccination coverage, total winter and seasonal excess all-cause (AC) death rate in person aged ≥65 years for 31 influenza seasons, 1970–2001 in Italy

Influenz seasons	Dominant viral subtype	Percentage of dominant virus	Italian elderly ≥65 years of age				
			Vaccination coverage (%)	Total Italian winter mortality (December–March)	Excess AC death (regression model)	Excess AC death rate/100000	Percentage Excess AC mortality/all winter deaths
1970/1971	B			131600	5600	95.1	4.3
1971/1972	A(H3N2)			136400	8700	141.4	6.4
1972/1973	A(H3N2)			150800	21400	341.1	14.2
1973/1974	A(H3N2)			138800	1100	17.9	0.8
1974/1975	A(H3N2)			160300	24800	377.0	15.5
1975/1976	A(H3N2)			152500	10300	153.3	6.8
1976/1977	A(H3N2)			155800	9900	144.7	6.4
1977/1978	A(H1N1)			150400	2400	34.3	1.6
1978/1979	A(H1N1)			148300	0	0	0.0
1979/1980	A(H3N2)			160000	8400	113.8	5.2
1980/1981	A(H3N2)	55	5	165600	13900	185.5	8.4
1981/1982	A(H3N2)	75	5	148000	0	0	0.0
1982/1983	A(H3N2)	88	6	163500	17200	232.6	10.5
1983/1984	A(H1N1)	93	6	151100	2900	39.4	1.9
1984/1985	A(H3N2)	89	7	155300	0	0	0.0
1985/1986	A(H3N2)	61	7	162900	13000	173.8	8.0
1986/1987	A(H1N1)	91	8	149800	0	0	0.0
1987/1988	B	61	10	147900	2400	31.1	1.7
1988/1989	A(H1N1)	97	14	151800	2700	33.0	1.8
1989/1990	A(H3N2)	96	18	165600	12500	150.8	7.6
1990/1991	B	74	22	158400	0	0	0.0
1991/1992	A(H3N2)	99	26	161800	4500	51.5	2.8
1992/1993	B	60	29	164200	6100	67.8	3.7
1993/1994	A(H3N2)	85	32	162800	4900	53.6	3.0
1994/1995	A(H3N2)	63	35	164500	4100	44.1	2.5
1995/1996	A(H3N2)	62	38	166300	2700	28.0	1.6
1996/1997	A(H3N2)	87	41	175400	9500	96.5	5.4
1997/1998	A(H3N2)	93	49	174800	10800	107.9	6.2
1998/1999	B[a]	58	55	189900	21400	210.1	11.3
1999/2000	A(H3N2)	99	61	183200	14500	140.2	7.9
2000/2001	A(H1N1)	99	61	162100	0	0	0.0
Average for all seasons				158400	7600	988	4.8

[a] Influenza B viruses and influenza A(H3N2) viruses co-dominated.

2.4. Statistical method

2.4.1. Excess mortality model

To estimate age-specific excess P&I and AC mortality rate for 31 influenza seasons, 1970–2001, we applied a Serfling-type regression model to monthly data [8], as described in the US study of trends in influenza-related mortality [12]. Briefly, we applied a seasonal regression model to a de-trended series of death rates, excluding values for December–April, to quantify the expected mortality in the absence of influenza activity. Monthly excess mortality rates were calculated as the observed minus expected mortality rate for all influenza *epidemic months*. *Epidemic months* were identified for each season based on those deaths where "influenza" was mentioned as the underlying cause of deaths (ICD-8 code 470–474 and ICD-9 code 487). Seasonal excess mortality was estimated as the sum of monthly excess mortality, after back adjusting for the true month length and time trend. We achieved an excellent fit for all age groups. All model terms included were statistically significant ($p < 0.0001$), but additional terms were not ($p > 0.05$).

2.4.2. Adjustment of seasonal excess mortality rates for population aging

We applied age-specific seasonal death rates by 5-year age group to the Italian population in 1975, considered a reference population. Age-standardized rates were then obtained by summing excess deaths in combined age groups of interest (65+, 65−74, 75–84) and dividing the sum by the 1975 population of that combined age group. Because the 85 years old and over age class data were not available by 5-year age group we used it as an open-ended category without standardization.

2.4.3. Statistical analysis of trends

To assess changes in excess mortality rates before and during the period of increasing vaccine coverage, we fit linear regression models for logarithmic (log 10) excess mortality rate on year, age, and age–year interaction for two periods, 1970–1986 (a period with no or low vaccine coverage) and 1987–2001 (a period with sharply rising vaccine coverage).

3. Results

3.1. Mortality impact of influenza among Italian elderly

Of the 31 influenza seasons studied in Italy, we identified a seasonal average of 99 excess AC deaths per 100,000 elderly ≥65 years (Table 1). Seasonal excess AC influenza deaths never represented more than 15% of the approximately 160,000 deaths that occur among the elderly each winter. Six of the 31 seasons (1978/1979, 1981/1982, 1984/1985, 1986/1987, 1990/1991 and 2000/2001) were not associated with measurable excess mortality. The most severe seasons were characterized by a predominance of A(H3N2) viruses. Overall, the average P&I death rates for season dominated by A(H3N2) influenza viruses was 4.2-fold greater than that of the 11 seasons dominated by A(H1N1) and B influenza viruses (Table 2).

The 3-year moving averages of unadjusted excess P&I and AC mortality excess rates in persons aged ≥65 years shows a increasing trend in the last decades of the study (Fig. 1: panels a and b). Moreover there was a pronounced change in the age distribution of influenza-related deaths within the elderly over time; for example, elderly >85 years of age accounted for 26%

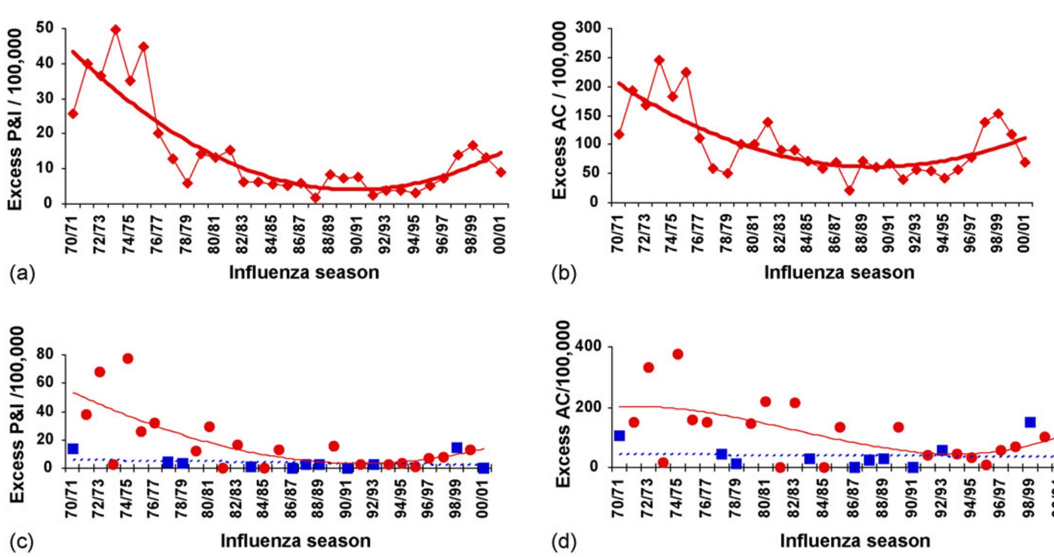

Fig. 1. Seasonal excess mortality rates among elderly ≥65 years of age, for individual seasons 1970–2001, Italy. P&I (left panels) and AC (right panels) excess death rates are indicated. (a and b) Unadjusted rates (red square) and (c and d) age-adjusted rates stratified by virus subtypes (red dots: A/H3N2; blue squares: B or A/H1N1). The red curve represents a 3-year moving average of all seasons (a and b) and A/H3N2-only seasons (c and d). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 2
Mean seasonal excess death rates per 100,000 from pneumonia and influenza (P&I) and all-cause (AC) in Italy 1970–2001 by age and dominant influenza subtype (crude and age adjusted)

Subtype	Excess mortality (100000^{-1}) 45–64 years		Excess mortality (100000^{-1}) >65 years (crude)		Excess mortality (100000^{-1}) >65 years (age-adjusted[a])	
	P&I	AC	P&I	AC	P&I	AC
A(H3N2)	1.04	7.53	19.37	127.69	18.34	118.81
A(H1N1)/B	0.15	2.09	4.61	46.44	4.00	40.77
Total	0.72	5.60	14.13	98.86	13.25	91.11

[a] Excess death rates are age-adjusted to the population of Italy in 1975 by 5-year age groups.

of excess AC deaths in the early 1970s but had reached 34% in the 1990s.

For the 20 influenza seasons dominated by A(H3N2) viruses, we estimated average excess P&I and AC death rates of 19 and 128 per 100,000, respectively, for the elderly ≥65 years (Table 2). These rates were about 20-fold higher than for the 45–64 age group (1 and 7 per 100,000 for P&I and AC, respectively). Adjusting for population aging among elderly did not change substantially the average of seasonal P&I and AC mortality rates for the entire three-decade study period (by 5–7%). However in the last decade of the study, population aging accelerated in Italy, and age-adjusted estimates were about 40% lower than crude estimate during this period. After adjusting for population aging, we found that the mortality impact of influenza A/H3N2-dominated seasons was four to seven times higher in the 1970s, the decade immediately following the emergence of the A/H3N2 subtype, as compared with the 1990s. Hence the marked declining pattern of mortality in the 1970s reflects strong and rapid adaptation to circulation of a novel influenza subtype.

For the 11 seasons dominated by influenza A(H1N1) and/or B viruses the average excess P&I and AC deaths rate were low compared to that of the A(H3N2) dominated seasons (Table 2) and no mortality trend was detected during the entire study period ($p > 0.05$).

3.2. *Trends in influenza-related mortality for 20 influenza A(H3N2) seasons*

The 3-year moving averages of unadjusted excess P&I and AC mortality excess rates in persons aged ≥65 years declined sharply from 1970 to mid-1980s, when there was an estimated <5% influenza vaccine coverage. Then P&I excess mortality rates subsequently reached a plateau and increased in the last study years (Fig. 1: panel c). AC mortality rates climbed from a low level in the mid-1980s to a level similar to that of the mid-1970s in the most recent years (Fig. 1: panel d).

Adjustment for population aging and greater frequency of the more virulent A(H3N2) dominant seasons could not completely account for the recent increase in influenza associated mortality rates. When vaccination rates accelerated rapidly, after 1987, no decline was detected in adjusted excess P&I and AC mortality among persons ≥65 years ($p = 0.2$) (Fig. 1: panels c and d).

The trend we observed in excess P&I mortality among all elderly for A(H3N2) seasons during the entire study period show important age group and temporal differences in adjusted excess mortality patterns. For persons aged 65–74 and 75–84 years the excess P&I mortality rates fell by 60% from 1970 to 1980 ($p = 0.03$ and 0.04, respectively), but reached a plateau thereafter, with a slight increase in most recent years (Fig. 2: panels a–d). A similar pattern was observed for persons aged 45–64, an age group with lower vaccination coverage (data not shown). Among the very elderly (≥85 years old), excess P&I mortality rates and excess AC mortality rates tended to increase more substantially over the last decade (Fig. 2: panels e and f).

To quantify changes in excess mortality rates before and during the period of increasing vaccination coverage, we explored two periods, 1970–1986 and 1987–2001, comprising, respectively, 12 and 8 A(H3N2) seasons (Table 3). We used the age range 65–84 years where we could adjust for population aging by 5-year age intervals (avoiding open age intervals after 85), and fit separate trend models for P&I and AC mortality. For the first period (1970–1986) we found a

Table 3
Trends in excess mortality rates in Italian elderly (65–84[a] years) for 20 influenza A(H3N2)-dominated seasons during 1970–2001, stratified by period of low and rapidly increasing vaccine use

Time period	P&I			All-cause		
	%Annual change	%Total change during the time period	*p*-Value	%Annual change	%Total change during the time period	*p*-Value
Low vaccine use (<8%) 1970–1986 (12 A(H3N2) seasons)	−9.1	−146	<0.0001	−7.8	−120	0.002
Rapidly increasing vaccine use 1987–2001 (8 A(H3N2) seasons)	2.1	29	0.36	−0.9	−13	0.75

[a] Four 5-year age group categories combined in a single trend model, 85 and over were excluded because it is an open-ended category.

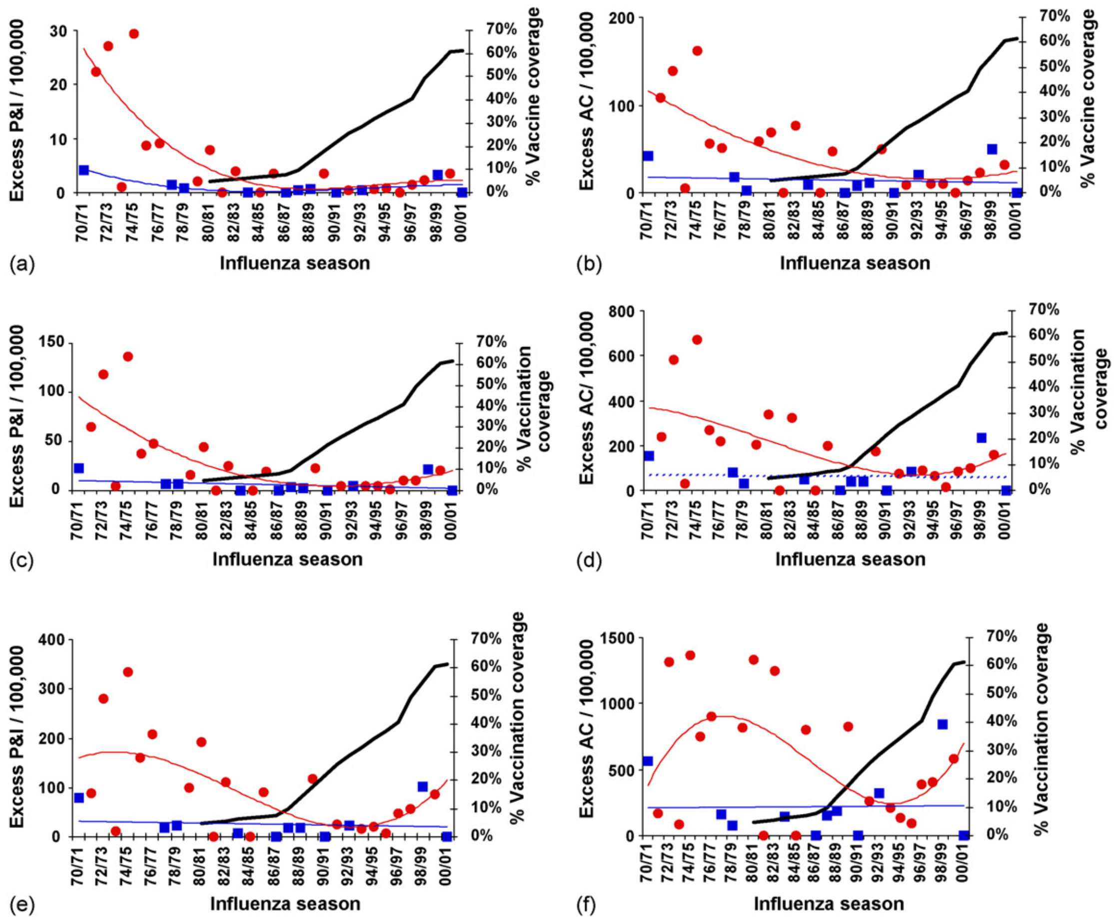

Fig. 2. Age-specific seasonal excess mortality rates among elderly ≥65 years of age, for individual seasons 1970–2001, Italy. Age-adjusted estimates of seasonal excess P&I (left panels) and all-cause (AC) (right panels) mortality rates (per 100,000) among person 65–74 (a and b) and 75–84 years of age (c and d). Unadjusted excess death rates (per 100,000) are shown for people ≥85 years (e and f). Red dots indicate seasons dominated by influenza A(H3N2) viruses, and blue squares for seasons dominated by influenza A(H1N1) and/or B viruses. The black solid line shows influenza vaccination coverage rates in people over 65, and the red line represents a 3-year moving average of all seasons (a and b) and A/H3N2-only seasons (c and d). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

significant declining trend over time for both P&I and AC excess mortality rates ($p \leq 0.002$). By contrast, we found no evidence of any trend during the second period when vaccine coverage rose (1987–2001), either for P&I ($p = 0.36$) or AC ($p = 0.75$) mortality.

3.3. Sensitivity analysis on trends findings

We conducted additional analyses to assess whether our results were sensitive to the choice of the subset of seasons included in the trends analysis. One influenza season in particular, 1998–1999, had high excess mortality impact, but curiously was defined as an influenza B season (in which influenza B represented 58% of all isolates). Interestingly, a high proportion of co-circulating A(H3N2) viruses was reported in that same season (42%), suggesting that this season may be misclassified. When we included this season as a misclassified A(H3N2) season in the trend analyses, it only marginally affected our findings: we still could not detect any significant trend in influenza-related mortality rates in the recent period of rapidly increasing vaccine coverage.

4. Discussion

We have studied the influenza associated excess mortality in the Italian elderly population, from 1970 to 2001, and sought to evaluate the mortality benefits of the influenza vaccination program. Although the program was initiated in the late 1970s, we estimate that it only achieved coverage greater than 50% among the elderly by the late 1990s, based on vaccine distribution data. The Italian National Vaccines Plan for the year 2000 [27] had established a goal of 75% coverage among persons 65 years or older, considerably higher than the actual ∼60% reported from the Ministry of Health in recent years [23].

After carefully adjusting for population aging and stratifying by dominant influenza sub-type to account for increasing frequency of circulation of the virulent A(H3N2) viruses in recent years, we found no evidence of reduction in influenza-related mortality in the last 15 years, despite the concomitant increase of influenza vaccination coverage from ∼10% to ∼60%. Furthermore, the proportion of all winter deaths attributable to influenza as AC excess mortality was 4.9% on average, and always less than 15% for any season studied. Our findings are consistent with those of a recent US trend study using the same methodology as ours, where the proportion of all winter deaths attributable to influenza was 5% on average [12]. These findings cannot be reconciled with conclusions from cohort studies which state that influenza vaccination can reduce all winter mortality by 50% in those vaccinated [17,18]. The US trend study found that the increase in vaccination coverage (from 15–20% before 1980 to 65% in 2001) was not associated with a decline in influenza death rates, also in line with our results. Moreover, in both the US and Italian trend studies, findings were confirmed by a similar mortality pattern observed for persons aged 45–64, an age group with lower vaccination coverage.

In the years immediately after the 1968 pandemic, we observed a sharp decline in influenza-related deaths among people aged 65–74 and 75–84, that could be explained by the acquisition of natural immunity to these viruses during the first decade of A(H3N2) emergence [28]. By the late 1980s, as vaccination coverage increased, there were relatively fewer influenza-related deaths in the “younger elderly” that could be prevented by vaccination, i.e. the 65–74 (an average death rate of 17 per 100,000 per season) and 75–84 age groups (an average death rate of 83 per 100,000 per season). By contrast, the “very elderly” accounted for an increasing proportion of influenza deaths over time; in particular, people aged 85 and over have a risk of influenza-related death of 314 per 100,000 per season.

4.1. Caveats

In the trend analysis, we considered the possibility that the elderly population in the 1990s were more frail and likely to die of influenza than their age peers of the 1980s for reasons such as increased medication use and living longer with chronic diseases. Such a cohort effect could mask mortality benefits of the vaccine. However, we rejected the possibility of this effect by comparing summer mortality rates over time, where summer mortality is good control of cohort effects unrelated to influenza. We found that for all elderly age groups, summer AC mortality rates declined steadily after 1980 (by ∼1% every year, $p < 0.001$), which strongly suggests that the current elderly population is actually less “frail” than the elderly population of earlier years. If we had further adjusted for such cohort effects, it would have resulted in even less reduction in influenza-related mortality during the years of increasing vaccination coverage.

Another caveat relates to possible overestimation of the influenza vaccination coverage before 1999, as it was derived from the total number of doses distributed by general practitioners and local health departments. Yet, our data are consistent with limited regional studies that have surveyed vaccination rates in 1995 and 1999 [15,16,29]. Additionally, our data are in agreement with other studies of influenza vaccine sales in Italy, which documented a 2.8-fold increase in vaccine use between 1990 and 2000 [30,31], closely paralleling the 2.7-fold increase that we report in the same period (Table 1). Hence in Italy as in several other countries in Europe and North America, vaccine coverage among the elderly has increased from <10% to 60% over the last 10–20 years [30]. Such a large change in vaccine coverage should be sufficient to detect a mortality benefit of the vaccination program, if there was truly one.

Lastly, there are other caveats that we could not completely address in this study and that might have contributed to the apparent lack of benefit of the vaccination program. For example, virulence of influenza A(H3N2) viruses could have been increasing over time; if this was the case, it could have masked true vaccine benefits.

The results of this Italian study corroborate recent findings in a similar US-based study [12] and suggest that current strategies focused on vaccinating the elderly have not been associated with reduced seasonal influenza-related mortality in this age group, as might be expected based on the high vaccine effectiveness measured by cohort studies [17,18]. One possibility for reconciling these findings is the existence of a systematic bias towards lower vaccination rates in the frailest elderly, i.e. the most susceptible to seasonal death [20]. Indeed, such a bias has been documented in a recent US cohort study [20].

Vaccine benefits are commonly evaluated by demonstrating a reduction of morbidity and mortality in the years after their introduction. The lack of mortality reduction observed in US and Italian trends studies support a long-standing concern that the very elderly do not respond well to influenza vaccine, possibly due to immune senescence [22,32]. This is especially pertinent for elderly over 75, an age group that account for 3/4 of all influenza related deaths in recent years ([12], this study). The lack of observed vaccine benefit has helped fuel a debate about ways to improve the current strategy to control influenza and mitigate its impact [33,34]. Possible strategies include the development of more immunogenic vaccines, multiple or higher antigen doses in vaccines [35], or increased use of antivirals. In Italy, more immunogenic vaccine with novel adjuvants have been introduced since 1997 [36–38], but it is too early to evaluate their population impact. Alternatively, indirect protection of the elderly may be achieved through efforts to reduce influenza transmission in the community. Vaccination of transmitter groups, such as care givers or school children, would lead to decreased transmission to the frailest age groups [39].

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