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Influenza vaccine uptake in the elderly population: Individual and general practitioner's determinants in Central Italy, Lazio region, 2016–2017 season

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ABSTRACT

Background: Elderly people are a priority target group for influenza vaccination and their decision to be vaccinated might partly depend on advice received from general practitioners (GP). This study aims to investigate the association between influenza vaccine uptake in the elderly residents in the Lazio region of Italy and the demographic and professional characteristics of their GPs, taking simultaneously into account the elderly's individual characteristics.

Methods: We used data retrieved from different administrative sources to retrospectively analyse the cohort of 1,255,657 elderly residents aged ≥65 years who were alive and registered in the regional healthcare service at the beginning of the 2016–2017 influenza vaccination campaign (1 Oct. 2016–31 Jan. 2017). We assessed influenza vaccine uptake at the end of the vaccination campaign and evaluated its association with both individual and GP-related characteristics through a multilevel Poisson regression models accounting for clustering at physician level.

Results: Overall, vaccination coverage at the end of vaccination campaign was 50.6%. Elderly residents who were male, older, vaccinated in the previous seasons, living in smaller provinces, and spending more money for specialist medical care showed a significantly increased probability to be vaccinated. Vaccine uptake was also significantly higher in the elderly residents assisted by GPs who got master's degree more recently, assisted a relatively high proportion of elderly patients, received influenza vaccination, had a computer assistant, and were associated with other physicians.

Conclusions: Our results indicate that influenza vaccination coverage in the elderly residents of the Lazio region is still unsatisfactorily low. We identified several determinants of influenza vaccine uptake, related to both individual and GP characteristics. Understanding how GP characteristics affected influenza vaccine uptake in the elderly population might provide insight on GPs' attitudes and concerns regarding influenza vaccination, allowing the implementation of targeted evidence-based interventions to sensitise GPs and increase vaccination coverage.

1. Introduction

In the European economic area (EEA), excess mortality from all causes was reported by the majority of 20 reporting countries during the influenza season 2017–18 and was mainly observed in people aged 65 years or older [1].

In Italy, it was estimated that 5.4 million individuals (almost 10% of the country's population) got influenza-like-illness (ILI) in the season 2016–2017 [2]. On average, influenza disease was

Abbreviations: EEA, European economic area; ILI, influenza like illness; WHO, World Health Organization; ECDC, European Centre for Disease Prevention and Control; GP, general practitioner; LHU, local health unit; RHA, regional health assistance; HIS, hospital information system; OIS, outpatients information system; REP, registry of exempt patients; FVIS, flue vaccination information system; GPIS, GP information system; CCI, Charlson comorbidity index; NHS, national health system; ML, multilevel; VRR, vaccination rate ratio; CI, confidence interval.

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estimated to cause more than 20,000 deaths during the flu season, about 90% of them in the elderly population [3].

The Italian national influenza vaccination program, in place since more than 20 years, has the main objective of protecting individuals at higher risk of influenza-related complications and deaths [4]. In Italy, the influenza vaccine is thus recommended and offered free of charge to at risk population groups, such as the elderly individuals aged 65 years and older, individuals between 6 months and 64 years of age with specific chronic conditions, pregnant women in their 2nd and 3rd trimester of gestation, health care workers, and people working in essential services [4]. According with recommendations from the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC), the Italian Ministry of Health established the 75% vaccination coverage as the minimum level to be reached in target groups [4]. Unfortunately, after the 2009/2010 pandemic season, Italy experienced a decline in influenza vaccination coverage (from 66% to 53% in the 2017/2018 season in the elderly population) [5]. This decline, considering also the high percentage of elderly residents (22.6% of the country's population), is the main reason why influenza still has a relevant burden on health and healthcare resources, especially in older individuals [6].

Recent studies have identified some potential determinants of missed influenza vaccination in the adult and elderly population. Among these, the lack of knowledge and understanding of the benefits of vaccination, demographic factors, inconsistent recommendations by providers, and uncertainties about vaccine effectiveness [7–9].

To increase vaccine uptake, some strategies were suggested, such as having a motivated lead member of staff, using additional prompts within the influenza vaccine management systems to identify eligible patients, and using phone calls and home visits to invite patients for vaccination [10–12]. This approach is supported by a study conducted in a local health unit in Southern Italy, which suggested the empowerment of primary care physicians through training and communication as an effective strategy [13]. Therefore, general practitioners (GP) seems to play an important role in the success of a seasonal influenza vaccination campaign [14].

The main objective of this study was to investigate the association between influenza vaccine uptake in the 2016–2017 season in the elderly population resident in the Lazio region and the demographic and professional characteristics of their GPs, taking simultaneously into account the individual characteristics of the elderly.

2. Methods

2.1. Study setting and design

The study was conducted in the Lazio region of central Italy, which is administratively divided in five provinces and had a population of about 5.9 million residents in January 2017 [15]. Of these, 21% were elderly people aged 65 years or more, most of them resident in the province of Rome (73%), in particular within the municipality of Rome (50%) [16]. Overall, the region is served by ten local health units (LHU) that are in charge of assessing needs and providing comprehensive health care to the resident population. Six LHUs serve the province of Rome (3 of them the municipality of Rome, the other 3 the other 120 municipalities within the province) and the remaining four serve the other provinces. Each resident may choose a GP, or paediatrician if aged 14 years and less, who is expected to provide most of the primary care. In most cases, influenza vaccine is administered free of charge to the elderly population (≥65 years) and people with comorbidities by their reference GP. Vaccine are distributed through regional and Local Health Authorities to GPs and are available also in pharmacies for the private market. The vaccination campaign generally starts in October every season. Before this date, GPs are invited to participate to an informative event organised by their reference LHU, during which they are updated about the results of the previous vaccination campaign and informed about recent recommendations introduced in the regional plan. Most of the GPs do not provide a specific invitation to their assisted population, and usually GPs offer vaccination to targeted population as they come to visit them for any reason. There is a basic financial incentive for GPs to vaccinate patients, provided they document the administered vaccinations in a dedicated electronic registry. Further pay incentives are provided in case GPs reach minimum levels of vaccination coverage in their elderly patients (i.e., 60% and 75%) [17].

We retrospectively analysed the cohort of elderly people aged 65 years and older who, on the 1st of October 2016, were alive, registered in the regional healthcare assistance (RHA) service, and resident in the Lazio Region since one year or more. The cohort was followed for the whole duration of the influenza vaccination campaign (1 Oct. 2016–31 Jan. 2017).

2.2. Data sources and procedures for defining the cohort

Different health administrative data sources, established by regional decrees and linkable through an anonymous identification code, were used to retrieve the data analysed in this study. In particular, we combined information from the following data sources, all managed by the Lazio region or LHUs and encompassing the entire regional territory:

- The Lazio region RHA registry, which includes demographic and residence information of all people living in the Lazio region and registered in the regional health service (97% of the whole population) [17].
- The hospital information system (HIS) of the Lazio region, active since 1995, where discharge records from all regional public and private hospitals are routinely entered, including information on admission and discharge dates, discharge status, up to six discharge diagnoses coded according to the International Classification of Disease, Clinical Modification, ninth version (ICD-9-CM), and up to six hospital procedures coded using ICD-9-CM [16].
- The outpatients information system (OIS), active since 2000, where consultations and procedures performed at regional outpatient centres, including hospitals, laboratories, and specialist medical studies, are recorded [16].
- The registry of exempt patients (REP), active since 2005, recording patients affected by specific diseases (e.g., diabetes, hypertension, autoimmune diseases, etc.) and entitled to freely access the related health care services (e.g., drugs prescriptions, laboratory exams, medical visits, etc.) [16].
- The flu vaccination information system (FVIS), active since 2000, where individual data on vaccinations administered by GPs and vaccination services of the LHUs are recorded [17]. These data include patient's demographic characteristics, date of vaccination, place of vaccination, type of vaccine administered, regional code of GP who administered vaccination, and reason for vaccination.
- The regional informative system on GPs (GPIS), active since 2000, including information about GPs' demographic and professional characteristics [16].

We first identified the study cohort through the RHA, which provided demographic and residence information of the elderly patients and the regional code of their assigned GP.

This dataset was linked to the HIS to obtain information on hospital admissions in the 12 months before the start of the vaccination campaign (1 Oct. 2015–30 Sep. 2016), and on hospital deaths occurred during the vaccination campaign (1 Oct. 2016–31 Jan. 2017). We then retrieved information about outpatient treatment in the 12 months before the start of the vaccination campaign from the OIS, and information about valid cost-exemptions for diagnostic exams and treatment of chronic diseases at the beginning of the study period from the REP. Information about influenza vaccination uptake during the study period and in the previous two seasons (2014–15 and 2015–16) was obtained linking data from FVIS. Finally, we used the GP's regional code to link data from the GPIS and retrieve information about physician's demographic and professional characteristics.

2.3. Outcome and explanatory variables

Time since October 1st 2016 to possible uptake of the influenza vaccine in the 2016–17 influenza season was the outcome of this study. Demographic and clinical characteristics of the elderly residents and demographic and professional characteristics of their physicians were evaluated as possible determinants of this outcome. In particular, we analysed the following explanatory variables: sex, age group (by 5-years intervals up to 89 and $\geq$90 years old), LHU of residence different from that of GP, province of residence, type of residence area (i.e., urban, semi-urban, or rural, according to the classification of municipalities by the Italian National Institute of Statistics [18]), influenza vaccine uptake in at least one of the previous two seasons, Charlson comorbidity index (CCI) based on hospital admissions in the previous 12 months [19], total expenses for outpatients specialist medical care in the previous 12 months, and number of cost-exemptions effective at October 1st 2016 for any chronic diseases and for specific chronic diseases considered at risk conditions for influenza [4]. We also evaluated as explanatory variables the following physicians' characteristics: sex, age group (<50, 50–54, 55–59, 60–64 and 65 years or more), LHU to which the GP is referring, years since master's degree, years since starting activities within the national health system (NHS), total number of followed individuals, percentage of treated patients aged 65 years or more, uptake of influenza vaccine in the 2016–17 season, availability of a computer assistant for secretarial activities (e.g., appointment scheduling and collection of requests for drugs prescriptions), and being part of an associative partnership (i.e., working alone or sharing the primary care activity with other GPs).

2.4. Statistical analysis

We described the characteristics of the elderly residents and their physicians using absolute frequencies and percentages. We also graphically described the weekly rate of influenza vaccine uptake together with the weekly ILI incidence in the season 2016–17, as estimated from the national surveillance system for the Lazio Region [2].

We estimated the influenza vaccination coverage at the end of the vaccination campaign through the Kaplan-Meier method (cumulative rate at 31 Jan. 2017), accounting for possible right-censoring before the end of follow-up in case of hospital death, and using days elapsed since the beginning of the vaccination campaign as underlying time scale.

The association between vaccine uptake and each explanatory variable was assessed through multilevel (ML) Poisson regression models accounting for the hierarchical structure of the data (i.e., random effect due to clustering at physician level). In order to account for the incidence rate modification during the vaccination campaign, models were run splitting follow-up time into four mutually exclusive intervals (i.e., 1–15, 16–55, 56–70, and 71–109 days from the start of the vaccination campaign). These intervals were chosen exploring the estimated hazard rate by days since the beginning of the vaccination campaign (Suppl. Fig. 1), assuming the hazard rate was constant within each interval. The variable identifying these time-intervals was included as a covariate into the models run on split data [20].

All variables significantly associated with vaccine uptake in univariate models ($p < 0.05$ by the log-likelihood ratio-test) were included in a ML multivariable model, except those highly correlated with other selected variables. In particular, in order to avoid collinearity, we did not include into the ML Poisson regression model the following variables: GP's reference LHU (highly associated with province of residence), CCI and cost-exemption for chronic diseases and at-risk conditions for influenza (highly correlated with expenses for specialist medical care), and physician's age and duration of activities within the NHS (highly correlated with time elapsed from master's degree).

The crude and adjusted vaccination rate ratios (VRR) and their 95% confidence intervals (CI) were used to describe the strength of the associations. Based on the ML multivariable model, we also estimated the variance between GPs and the intra-cluster correlation, the latter providing the proportion of residual variability unexplained by the variables included into the model that is due to physician level.

The statistical analysis was performed using Stata/SE version 15.1 (StataCorp LLC, Texas, USA).

2.5. Ethical aspects

This study was approved by the ethical committee of the Italian National Institute of Health (Prot. PRE/118/18 in date 16/03/2018).

3. Results

Of the 5,894,104 individuals who were resident in the Lazio region at the beginning of the study period (October 1st 2016), 5,517,248 (93.6%) were resident since one year or more and registered in the RHA service, 1,260,406 (22.8%) of whom aged 65 years or more. After excluding the elderly residents cured by GPs who had less than 30 reference patients (n = 3222; 0.03%), residents showing inconsistent data (n = 29; 0.002%), and residents with incomplete information (n = 1498; 0.1%), a total of 1,255,657 (99.6%) elderly residents assisted by the RHA service were included in our study (Fig. 1).

The vaccination campaign started in week 41 (10–16 October 2016), peaked in week 45 (7–13 November 2016), and ended in week 52 (26 Dec 2016- 1st Jan 2017) (Fig. 2). Few individuals were vaccinated after the ILI peak in week 52, until the week 5 (30 Jan-5 Feb) of 2017 (n = 1812; 0.3% of vaccinated). Overall, the influenza vaccination coverage in the elderly residents during the 2016/2017 season was 50.6%. About one/fifth of the vaccinated elderly received an adjuvanted vaccine (19.0% of the vaccinated elderly aged less than 75 years and 23.6% of those aged 75 years and older).

Demographic and clinical characteristics of the individuals included in the study are reported in Table 1. Most of the individuals were females (57.2%), were resident in an urban or semi-urban area (52.7% and 27.6%, respectively), and were vaccinated in the GP office (90.0%). According to the exemption registry, about one/third of the elderly residents were affected by at least one chronic disease (34.9%), most of them also presenting at-risk conditions for influenza (74.1%). Only 6197 (0.5%) hospital deaths were reported during the study period and 54.8% of the individuals received influenza vaccination in the previous season.

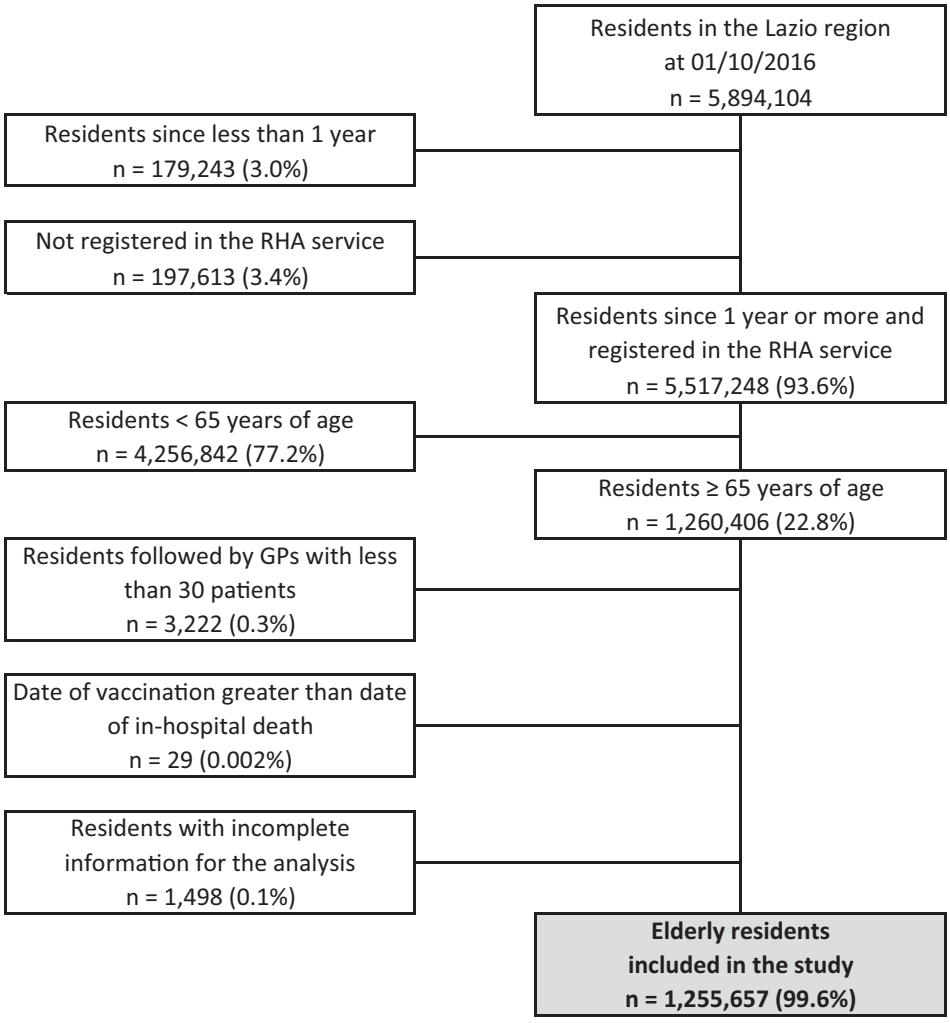

Fig. 1. Selection of residents included in the study. RHA, regional health assistance; GP, general practitioner.

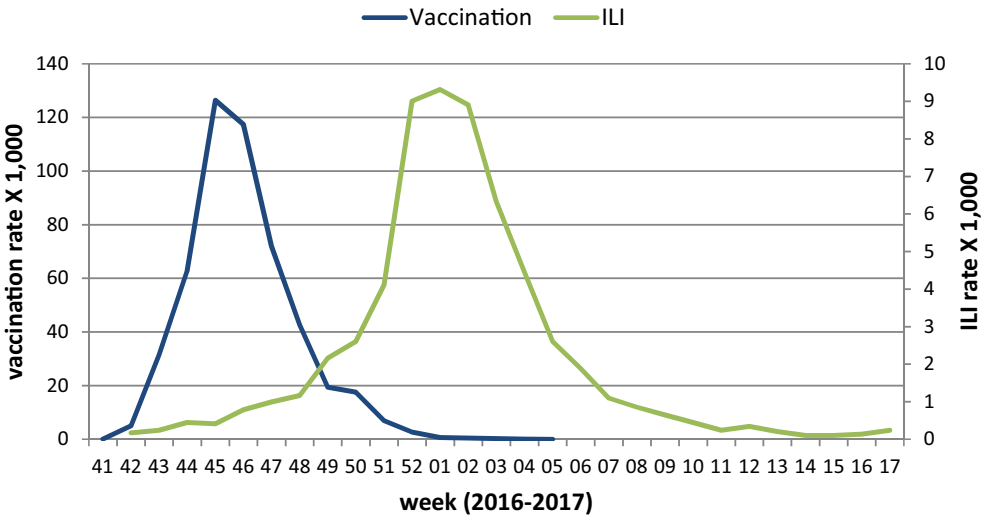

Fig. 2. Weekly influenza vaccination rate and ILI incidence (season 2016–17). ILI, influenza like illness.

The characteristics of the 4,337 GPs assisting the elderly residents are reported in Table 2. The majority were males (67.4%), were between 55 and 64 years of age (64.1%), and had more than one-fourth of assisted patients aged 65 years or more (57.2%). Moreover, 41.6% of GPs were vaccinated in the 2016/2017 season, 94.1% had a computer assistant supporting the administrative and logistical issues, and 82.5% were working in partnership with other physicians.

Table 1
Demographic and clinical characteristics of the elderly (≥65 years) resident in the Lazio region and assisted by the NHS at the beginning of the influenza vaccination campaign (1 October 2016).

	n	%
Sex		
Female	717,751	57.2
Male	537,906	42.8
Age group		
65–69 years	332,192	26.5
70–74 years	274,859	21.9
75–79 years	261,415	20.8
80–84 years	192,530	15.3
85–89 years	123,103	9.8
≥90 years	71,558	5.7
LHU of residence different from that of GP		
No	1,174,442	93.5
Yes	81,215	6.5
Province		
Rome	912,482	72.7
Viterbo	74,746	6.0
Rieti	39,326	3.1
Latina	118,465	9.4
Frosinone	110,638	8.8
Area of residence		
Urban	662,007	52.7
Semi-urban	346,109	27.6
Rural	247,541	19.7
Vaccination in previous 2 seasons[1]		
No	567,242	45.2
Yes	688,415	54.8
Charlson comorbidity index[2]		
No hospitalization	999,672	79.6
0	131,175	10.4
1	46,385	3.7
2	42,775	3.4
3	15,156	1.2
4–5	10,687	0.9
≥6	9807	0.8
Expenses for specialist medical care (Euros)[3]		
None	269,243	21.4
0.01–64.99	251,345	20.0
65.00–159.99	235,617	18.8
160.00–399.99	253,185	20.2
≥400.00	246,267	19.6
Exemptions for chronic diseases[4]		
None	807,281	64.3
1	276,055	22.6
2	103,549	9.0
≥3	68,772	3.3
Exemptions for at-risk conditions for influenza[4]		
None	931,845	74.2
1	267,039	21.3
≥2	56,773	4.5
Hospital death[5]		
No	1,249,460	99.5
Yes	6197	0.5
Place of vaccine administration		
GP office	571,633	90.0
Full/part time residential care institutions	7676	1.2
Home	55,177	8.7
Hospital	210	0.0
Other	490	0.1

GP, general practitioner.
[1] Vaccination in at least one of the previous two influenza seasons;
[2] Based on hospital admissions in the 12 months before the start of the vaccination campaign (1 Oct. 2015–30 Sep. 2016);
[3] Total amount spent in the 12 months before the start of the vaccination campaign;
[4] Valid cost exemptions at the beginning of the vaccination campaign (1 Oct. 2016);
[5] Hospital deaths occurred during the vaccination campaign from Oct. 2016 to Jan. 2017 (study follow-up).

Table 2
Characteristics of the general practitioners assisting the elderly residents at the beginning of the influenza vaccination campaign (1 October 2016).

	n	%
Sex		
Female	1427	32.6
Male	2946	67.4
Age group		
<50 years	230	5.3
50–54 years	536	12.3
55–59 years	1171	26.8
60–64 years	1630	37.3
≥65 years	806	18.4
Local health unit		
RM 1–6	3223	73.7
FR	379	8.7
LT	419	9.6
RI	121	2.8
VT	231	5.3
Years since master's degree		
<20 years	234	5.4
20–24 years	412	9.4
25–29 years	857	19.6
30–34 years	1195	27.3
35–39 years	1397	31.9
≥40 years	278	6.4
Years since starting activities within the NHS		
<10 years	454	10.4
10–19 years	1017	23.3
20–24 years	1003	22.9
25–29 years	828	18.9
30–34 years	321	7.3
≥35 years	750	17.2
Number of patients		
<1000	1435	32.8
1000–1249	855	19.6
1250–1449	817	18.7
1450–1499	724	16.6
≥1500	542	12.4
Percentage of patients ≥65 years		
<20%	706	16.1
20–24.9%	1167	26.7
25–29.9%	1421	32.5
30–34.9%	799	18.3
≥35%	280	6.4
Influenza vaccination in the 2016–17 season		
No	2552	58.4
Yes	1821	41.6
Computer assistant		
No	260	5.9
Yes	4113	94.1
Associative partnership		
No	766	17.5
Yes	3607	82.5

GP, general practitioner; NHS, national health system.

When considering the individual factors associated with influenza vaccination, according to multivariable analysis, we found that male sex (adjusted VRR = 1.11, 95% CI 1.10–1.12), having been vaccinated in the previous season (adjusted VRR = 8.36, 95% CI 8.17–8.55), living in smaller provinces other than that of Rome (adjusted VRR significantly higher than 1 for all provinces compared to Rome, except Rieti), and relatively high expenses for specialist medical care (annual expenses 0.01–64.99 euros vs none: adjusted VRR = 1.30, 95% CI 1.29–1.31; annual expenses ≥400 euros vs none: adjusted VRR = 1.50, 95% CI 1.48.1.51) were all characteristics significantly associated with the probability of being vaccinated (Table 3). This probability also increased with age until 85 years (80–84 years vs 65–69 years: adjusted VRR = 1.18, 95% CI 1.17–1.19) and then slightly decreased in individuals aged 85 years or more (85–89 years vs 65–69 years: adjusted VRR = 1.16, 95% CI 1.15–1.17; ≥90 years vs 65–69 years: adjusted VRR = 1.10, 95% CI 1.08–1.11).

The same analysis, referred to GP-related factors, showed a reduced probability to be vaccinated in the elderly residents assisted by GPs who earned their master's degree less recently

(20–24 years vs <20 years: adjusted VRR = 0.92, 95% CI 0.87–0.97; ≥40 years vs <20 years: adjusted VRR = 0.83, 95% CI 0.76–0.89) (Table 3). The probability to be vaccinated was higher in the elderly residents assisted by GPs who had a relatively high proportion of elderly patients (20–24.9% vs <20%: adjusted VRR = 1.07, 95% CI 1.02–1.11; ≥35% vs < 20%: adjusted VRR = 1.16, 95% CI 1.09–1.24), received influenza vaccination (adjusted VRR = 1.09, 95% CI 1.07–1.12), had a computer assistant (adjusted VRR = 1.13, 95% CI 1.06–1.20), and were associated with other physicians (adjusted VRR = 1.04, 95% CI 1.01–1.08) (Table 3).

It is of note that the GP level (i.e., overall GP characteristics) explained 8.8% (95% CI: 8.4–9.2) of the residual variability when

Table 3
Multilevel analysis of factors associated with influenza vaccine uptake in the season 2016–2017.

	Vaccinated		ML Crude VRR*	ML Adjusted VRR*
	n	VC** (95% CI)	(95% CI)	(95% CI)
Individual characteristics				
Sex				
Female	355,519	49.9 (49.5–49.7)	1	1
Male	279,667	52.1 (51.9–52.2)	1.08 (1.07–1.09)	1.11 (1.10–1.12)
Age group				
65–69 years	116,101	35.0 (34.8–35.1)	1	1
70–74 years	129,152	47.0 (46.8–47.2)	1.51 (1.49–1.52)	1.07 (1.06–1.08)
75–79 years	149,450	57.2 (57.0–57.4)	2.02 (2.00–2.04)	1.15 (1.14–1.16)
80–84 years	121,145	63.0 (62.8–63.3)	2.34 (2.32–2.37)	1.18 (1.17–1.19)
85–89 years	77,953	63.5 (63.3–63.8)	2.37 (2.34–2.40)	1.16 (1.15–1.17)
≥90 years	41,385	58.1 (57.7–58.5)	2.07 (2.04–2.11)	1.10 (1.08–1.11)
LHU of residence different from that of GP				
No	594,971	50.7 (50.6–50.8)	1	NI
Yes	40,215	49.6 (49.2–49.9)	1.00 (0.98–1.02)	
Province				
Rome	448,338	49.2 (49.1–49.3)	1	1
Viterbo	38,925	52.1 (51.8–52.5)	1.06 (1.01–1.12)	1.05 (1.01–1.09)
Rieti	20,997	53.5 (53.0–54.0)	1.11 (1.05–1.18)	1.00 (0.95–1.05)
Latina	65,886	55.7 (55.4–56.0)	1.11 (1.07–1.16)	1.05 (1.02–1.08)
Frosinone	61,040	55.2 (54.9–55.5)	1.18 (1.13–1.23)	1.04 (1.01–1.07)
Area of residence				
Urban	325,905	49.3 (49.2–49.4)	1	NI
Semi-urban	178,661	51.7 (51.5–51.9)	1.01 (0.98–1.03)	
Rural	130,620	52.8 (52.6–53.0)	1.00 (0.98–1.03)	
Vaccination in previous 2 seasons[1]				
No	89,039	15.7 (15.6–15.8)	1	1
Yes	546,147	79.5 (79.4–79.6)	9.17 (8.97–9.37)	8.36 (8.17–8.55)
Charlson comorbidity index[2]				
No hospitalization	492,410	49.3 (49.2–49.4)	1	NI
0	71,692	54.7 (54.4–55.0)	1.18 (1.17–1.19)	
1	27,840	60.2 (59.8–60.7)	1.35 (1.33–1.37)	
2	24,027	56.4 (55.9–56.9)	1.22 (1.20–1.24)	
3	9128	60.7 (59.9–61.5)	1.35 (1.32–1.38)	
4–5	6313	59.8 (58.9–60.7)	1.33 (1.30–1.37)	
≥6	3776	38.9 (38.0–39.9)	0.72 (0.70–0.75)	
Expenses for specialist medical care (Euros)[3]				
None	87,308	32.4 (32.3–32.6)	1	1
0.01–64.99	124,200	49.5 (49.3–49.7)	1.73 (1.72–1.75)	1.30 (1.29–1.31)
65.00–159.99	129,175	54.9 (54.7–55.1)	2.04 (2.02–2.07)	1.40 (1.39–1.41)
160.00–399.99	147,839	58.5 (58.3–58.7)	2.29 (2.26–2.31)	1.49 (1.47–1.50)
≥400.00	146,664	59.7 (59.5–59.9)	2.39 (2.37–2.42)	1.50 (1.48–1.51)
Exemptions for chronic diseases[4]				
None	380,320	47.2 (47.0–47.3)	1	NI
1	149,710	54.3 (54.1–54.5)	1.23 (1.22–1.24)	
2	61,262	59.2 (58.9–59.5)	1.42 (1.41–1.44)	
≥3	43,894	64.0 (63.6–64.3)	1.63 (1.61–1.65)	
Exemptions for at-risk conditions for influenza[4]				
None	446,210	47.9 (47.8–48.0)	1	NI
1	153,188	57.5 (57.3–57.7)	1.31 (1.30–1.32)	
≥2	35,788	63.2 (62.8–63.6)	1.54 (1.53–1.56)	
GP characteristics				
Sex				
Female	181,884	50.2 (50.0–50.4)	1	NI
Male	453,302	50.8 (50.7–50.9)	1.00 (0.97–1.03)	
Age group				
<50 years	27,044	53.2 (52.7–53.6)	1	NI
50–54 years	70,099	51.4 (51.2–51.7)	0.93 (0.87–0.99)	
55–59 years	167,376	51.2 (51.0–51.4)	0.93 (0.87–0.99)	
60–64 years	248,852	50.6 (50.5–50.8)	0.89 (0.84–0.95)	
≥65 years	121,815	49.0 (48.8–49.2)	0.81 (0.76–0.87)	
Local health unit				
RM 1–6	449,235	49.2 (49.1–49.3)	1	NI
FR	61,021	55.2 (54.9–55.5)	1.24 (1.18–1.29)	

(*continued on next page*)

Table 3 (*continued*)

	Vaccinated		ML Crude VRR*	ML Adjusted VRR*
	n	VC** (95% CI)	(95% CI)	(95% CI)
LT	65,623	55.7 (55.4–56.0)	1.22 (1.17–1.27)	
RI	20,638	53.4 (52.9–53.9)	1.13 (1.05–1.22)	
VT	38,669	52.2 (51.8–52.5)	1.12 (1.05–1.18)	
Years since master's degree				
<20 years	27,479	54.7 (54.2–55.1)	1	1
20–24 years	53,190	52.1 (51.8–52.4)	0.90 (0.84–0.96)	0.92 (0.87–0.97)
25–29 years	115,512	50.8 (50.6–51.0)	0.89 (0.84–0.94)	0.92 (0.88–0.96)
30–34 years	179,648	50.6 (50.5–50.8)	0.87 (0.82–0.92)	0.91 (0.87–0.95)
35–39 years	216,991	50.3 (50.2–50.4)	0.84 (0.80–0.89)	0.90 (0.86–0.94)
≥40 years	42,366	48.0 (47.7–48.3)	0.75 (0.68–0.82)	0.83 (0.76–0.89)
Years since starting activities within the NHS				
<10 years	51,356	52.0 (51.7–52.3)	1	NI
10–19 years	133,067	52.0 (51.8–52.2)	0.97 (0.93–1.03)	
20–24 years	143,486	49.3 (49.1–49.5)	0.89 (0.85–0.94)	
25–29 years	135,199	50.9 (50.7–51.1)	0.93 (0.89–0.98)	
30–34 years	52,600	52.2 (51.9–52.5)	0.98 (0.92–1.04)	
≥35 years	119,478	49.4 (49.2–49.6)	0.87 (0.82–0.93)	
Number of patients				
<1000	126,956	51.4 (51.2–51.6)	1	NI
1000–1249	129,154	50.4 (50.2–50.6)	1.01 (0.97–1.05)	
1250–1449	142,097	50.1 (50.0–50.3)	1.00 (0.96–1.04)	
1450–1499	133,315	50.1 (49.9–50.3)	1.01 (0.97–1.06)	
≥1500	103,664	51.6 (51.3–51.8)	1.05 (1.01–1.10)	
Percentage of patients ≥65 years				
<20%	63,514	50.0 (49.7–50.3)	1	1
20–24.9%	159,928	51.2 (51.0–51.4)	1.08 (1.03–1.13)	1.07 (1.02–1.11)
25–29.9%	225,806	50.8 (50.6–50.9)	1.07 (1.02–1.12)	1.07 (1.03–1.12)
30–34.9%	140,278	50.0 (49.8–50.2)	1.06 (1.01–1.11)	1.11 (1.06–1.15)
≥35%	45,650	51.2 (50.8–51.5)	1.14 (1.06–1.22)	1.16 (1.09–1.24)
Influenza vaccination in the 2016–17 season				
No	355,192	49.1 (49.0–49.3)	1	1
Yes	279,994	52.7 (52.5–52.8)	1.14 (1.11–1.17)	1.09 (1.07–1.12)
Computer assistant				
No	29,565	46.8 (46.4–47.2)	1	1
Yes	605,621	50.8 (50.7–50.9)	1.20 (1.10–1.30)	1.13 (1.06–1.20)
Associative partnership				
No	76,807	48.6 (48.4–48.9)	1	1
Yes	558,379	50.9 (50.8–51.0)	1.09 (1.04–1.14)	1.04 (1.01–1.08)
Variance between GPs				0.13 (0.11–0.15)
Intra GP correlation (%)[5]				8.47 (8.10–8.86)

GP, general practitioner; NHS, national health system; CI, confidence interval; ML, multilevel; VRR, vaccination rate ratio.

* ML Poisson regression models accounting for the random effect due to reference GP. Model were run splitting follow-up time into four mutually exclusive intervals (i.e., 1–15, 16–55, 56–70, and 71–109 days from the start of the vaccination campaign), within each of them we assumed vaccination rate was constant. The variable identifying these time-intervals was included as a covariate into the models [20];

** VC, vaccination coverage (%) at the end of the campaign (31 Jan. 2017) estimated through the Kaplan-Meier method (cumulative failure rate); NI, not included in the multivariable model ($p > 0.05$ in univariate model or collinear with other variables).

[1] Vaccination in at least one of the previous two influenza seasons;

[2] Based on hospital admissions in the 12 months before the start of the vaccination campaign (1 Oct. 2015–30 Sep. 2016);

[3] Total amount spent in the 12 months before the start of the vaccination campaign (1 Oct. 2015–30 Sep. 2016);

[4] Valid cost exemptions at the beginning of the vaccination campaign (1 Oct. 2016);

[5] Proportion of residual variability unexplained by the variables included in the model that is due to GP characteristics.

only individual variables were included in the multivariable model. Adding the available GP-related variables to the model slightly reduced this estimate (intra GP correlation = 8.5%, 95% CI: 8.1–8.9).

4. Discussion

We identified several determinants of influenza vaccine uptake in the elderly population, related to both individual and GP characteristics.

Individual characteristics included gender (males were more prone to vaccination), older age, living in smaller and less urbanised provinces, and seeking specialist medical care. However, the stronger predictor of influenza vaccine uptake was found to be vaccination in the previous seasons, which reflects the individual propensity to vaccination determined by characteristics other than those analysed in this study. In general, these results are in line with studies conducted in different countries where, among others, suffering from medical conditions at risk for influenza complications and especially increased age were found to be factors positively associated with vaccine uptake [9,21,22].

We also found that the probability of being vaccinated was higher in the elderly residents assisted by GPs who were more recently graduated, vaccinated, working in association with other physicians and with a computer assistant, and assisting a relatively high proportion of elderly patients.

To our knowledge, our study is the first reporting also results on the association between influenza vaccine uptake and GP's demographic and professional characteristics. Understanding how these characteristics contribute to increase influenza vaccine uptake in the elderly population provides insight on GPs' attitudes and concerns regarding influenza vaccination. This allows for the exploration of possible solutions to help public health authorities on implementing targeted evidence-based interventions to sensitise GPs and increase vaccination coverage. However, our results based

on intra-GP correlation also suggest that other GP-related factors, which were not investigated in this study, accounted for most of the GP-related variability.

As recognized in other countries and settings, receiving influenza vaccination recommendation from physicians is a strong enabling factor for influenza vaccine uptake [9,23]. Efforts should therefore be made to improve the involvement of GPs, especially in the province of Rome, where we observed a reduced vaccination coverage in the elderly population.

It has been shown that increasing influenza VC, especially in the elderly, is possible. Some countries, as the UK and the Netherlands, have specific guidelines [24–26] in place and are the only European countries that have reached - or are close to reaching - the 75% target vaccination rate in elderly individuals [27]. Based on these experiences, measures for improving influenza vaccination programme efficiency have been suggested for being implemented at EU level, such as including patient eligibility and notification, logistics, record-keeping, and responding to questions that are frequently asked by patients [28].

However, further research is also necessary to assess needs and evaluate communication channels for the efficient provision of vaccine-related information to private physicians, as well as to identify effective patient recall and reminder systems.

In the last decade, Italy has faced a decline in the coverage of influenza and other vaccinations in all age groups, with most regions falling below the goals requested by the Ministry of Health and by EU and international public health authorities [4,5]. Several explanations have been proposed for the decreased vaccine coverage: the underestimation of infection-related severe harms of the disease by physicians, and an increased concern on vaccine safety by the general population [29]. Moreover, other events were considered to have played a major role in decreasing the influenza vaccination coverage in the elderly in Italy: the cessation of incentives to GPs in some Italian regions in 2013 (when an important drop in national vaccine coverage was registered) [5], and a media alert released in November 2014 season, in the middle of the vaccination campaign, regarding the potential causal relationship between influenza vaccination and deaths in some elderly individuals (this claim was 2 weeks later disproved) [30].

Despite a slight increase in the seasonal influenza vaccination coverage in elderly individuals in the past three years [5], our results confirm that influenza vaccination coverage in this target group is still unsatisfactorily low, much below the expected 75%.

Measures implemented at GP-level (e.g., reminder systems such as personal letters to patients and effective systems to monitor vaccine uptake) and local health authority level (e.g., expanded locations like pharmacy venues, target-group oriented education strategies, and media awareness campaigns) may help to increase influenza vaccination coverage among elderly people [12,31,32], especially if applied in combination, and should therefore be enhanced in the Lazio region.

At the same time, the production and utilisation of improved seasonal influenza vaccines with greater effectiveness should be given a high priority [33]. Recently, the introduction of new influenza vaccines, such as high-dose and adjuvanted cell based vaccines, hold promise for improving the health and well-being of the elderly population [34–38].

4.1. Strengths and limitations

In the Lazio region, the presence of an influenza vaccination registry and up-to-date regional administrative data allowed to evaluate and identify some drivers of influenza vaccine uptake in the elderly residents assisted by the regional health service. Our study was highly representative of this important target group. In fact, complete and consistent information was available for the analysis for more than 99% of the study population.

The analysis was conducted using a time-to-event statistical approach that accounted for possible right-censoring due to deaths occurred before the end of follow-up. This allowed more accurate estimates of vaccination coverage, avoiding the bias due to disregarding the effective exposure time of the elderly residents during the vaccination campaign. It is worthwhile to note that we were not able to retrieve information about out-of-hospital deaths, which were estimated to account for 53.9% of all deaths occurring in the elderly population of the Lazio region during the vaccination months of 2016 (personal communication). As a consequence, time of exposure during the vaccination campaign might have been overestimated, thus leading to underestimates of vaccination coverage. However, a sensitivity analysis, which was conducted assuming all the 7240 expected out-of-hospital deaths as occurred in unvaccinated elderly at mid vaccination campaign, yielded an estimated vaccination coverage of 50.7%, very close to that derived from original data (50.6%). Therefore, disregarding out-of-hospital deaths did not greatly affect the overall estimate of vaccination coverage, although a possible bias could still have affected estimates of the association between vaccine uptake and variables whose categories are likely to have a significantly different risk of out-of-hospital deaths (e.g., comorbidity).

Our analysis did not account for vaccines that were privately purchased and administered outside the public circuit. This could have led to underestimate vaccination coverage, although, being the elderly individuals entitled to be vaccinated free of charge, the proportion of those who paid out-of-pocket for influenza vaccine is likely to be negligible.

Part of the elderly residents were not vaccinated by their GP, at the physician's office or at home. This suggests that, in these cases, the role played by GPs on their decision could have been mitigated. However, this proportion is very small (1.3%) and we do not expect that this affected the evaluation of the influence of GPs characteristics on influenza vaccine uptake.

Finally, the proportion of elderly people affected by chronic diseases is likely to be underestimated in our study. In fact, it only accounts for valid cost exemption at the beginning of the vaccination campaign. This proportion would have probably resulted higher and consistent with national and regional figures [39,40] if data about disease-specific drugs prescriptions were also available.

5. Conclusions

Our results confirm that GPs are likely to play a role in the elderly people's decisions about influenza vaccine uptake. Although influenza vaccination coverage in the elderly individuals living in the Lazio region slightly increased in the past three years, its level is still below the expected threshold and measures to improve it are needed. Regional guidelines should be reinforced and revised by recommending specific actions at both GP and local health authority level. At GP-level, these should include the utilisation of invitation letters or other type of reminders (e.g., phone calls) and effective systems to monitor vaccine uptake. At local health authority level, these should include the improvement of the existing vaccine-management system and participation of GPs to informative events, the revision of the incentive pay plan for GPs, the provision of more detailed, real time and granular data on vaccination coverage, the organization of media awareness campaigns, and the offer of expanded locations with free access to the elderly people and other target populations for influenza vaccination (e.g., pharmacy venues).

6. Contributors

MFab, CR, PP, and FC conceived the study. All authors provided substantial contribution to the study design. EV, MFar, AB, SM, and FC retrieved and managed data. MFab, PP and FC performed the statistical analysis. MFab, CR, PP and FC drafted the manuscript. All authors critically revised the manuscript, approved the final version, and attest they meet the ICMJE criteria for authorship.

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Declaration of Competing Interest

The authors have no conflicts of interest in relation to the study presented in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.07.054.

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