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ORIGINAL ARTICLE

Pandemic and seasonal vaccine coverage and effectiveness during the 2009–2010 pandemic influenza in an Italian adult population

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Abstract
Objectives To evaluate the response to pandemic vaccination and seasonal and pandemic vaccine effectiveness (VE) in an Italian adult population, during the 2009–2010 influenza season.
Methods Data were recorded by interviewing 19,275 subjects (≥35 years), randomly recruited from the general population of the Moli-sani project. Events [influenza-like illness (ILI), hospitalization and death], which had occurred between 1 November 2009 and 31 January 2010 were considered. VE was analyzed by multivariable Poisson regression analysis.
Results *Pandemic* vaccine coverage was very low (2.4%) in subjects at high-flu risk, aged 35–65 years ($N = 8{,}048$); there was no significant preventive effect of vaccine against ILI.
Seasonal vaccine coverage was 26.6% in the whole population (63% in elderly and 21.9% in middle-aged subjects at high-flu risk). There was a higher risk to develop ILI in middle-age [VE: −17% (95% CI: −35,−1)] or at high flu-risk [VE: −17% (95% CI: −39, 2)] vaccinated groups.
Conclusions Coverage of pandemic vaccine was very low in a Southern Italy population, with no protective effect against ILI.

On behalf of the Moli-sani Project Investigators, the Moli-sani Project Investigators are listed in the "Appendix".

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Introduction

In April 2009, a new influenza A virus appeared (A/California/04/2009) and on 11 June 2009 (CDC 2009a, b), the outbreak of the influenza A (H1N1) virus was declared "pandemic" by the World Health Organization (Chan 2009). As a consequence, an international public health emergency was declared, by encouraging the health authorities to define a strategy with a vaccine created specifically against the circulating strain, as the virus was new and the population was not immune to it (CDC 2009c). This vaccination campaign was launched along with the yearly seasonal flu campaign and its main objectives were to directly mitigate transmission by recommending the vaccination for high-risk groups, ensure the general capacity to respond to the pandemic, and to protect the integrity of critical infrastructures (CDC 2009c). However, despite general consensus and recommendations for vaccination, the coverage in these groups was not high (Vírseda et al. 2010; Walter et al. 2011; Flunews 2010). The Italian Ministry of Health recommended the seasonal vaccination to all subjects older than 64 years and to those belonging to certain risk groups and also defined priority groups for pandemic vaccination owing to the fact that the vaccine was not immediately available for the entire population (MLSPS 2009; Rizzo et al. 2010a).

In Italy, seasonal vaccine was available from the beginning of October 2009, while pandemic vaccine from October 12; in the Molise Region, the latter was available from October 26 and was distributed in different steps, starting with young high-risk individuals. The pandemic vaccination campaign ended according to the national guidelines at the beginning of April 2010.

In Italy, the first cases of ILI were reported on 24 April 2009, but no significant signals of increased influenza activity were detected until middle October, and the epidemic curve reached its peak at middle November with an incidence of 12.9 cases per 1,000 served population (Flunews 2010; Rizzo et al. 2010a).

The evidence of vaccine efficacy, effectiveness and safety ("effects") (Simonsen et al. 2007; Jefferson et al. 2010) is still debated. Particularly, few data are available on the effectiveness of influenza vaccines in the elderly and in the population at high risk in Italy and this also reflects the difficulties of measuring vaccine effectiveness.

In the absence of randomised trials, observational studies are of interest to help guide health interventions aimed at reducing the impact of influenza in the population. Furthermore, these studies allow to gather relevant information on health status and behaviors against vaccination in the context of a pandemic, for planning communication strategies, not only to increase the vaccination coverage in the population, but also to improve perceptions, knowledge and attitudes during a possible new pandemic influenza.

The aim of this work was to evaluate seasonal and pandemic influenza vaccine coverage and effectiveness in an Italian adult population of Southern Italy, during the 2009–2010 pandemic influenza.

Methods

Study design and population

Seasonal and pandemic vaccine coverage and effectiveness against influenza-like illness (ILI), hospitalization and death were evaluated in the framework of a cohort study, the Moli-sani Project (Iacoviello et al. 2007; Centritto et al. 2009; Di Castelnuovo et al. 2011).

The cohort of the Moli-sani Project was recruited in the Molise region (a southern Italian region) from city hall registries by a multistage sampling. Exclusion criteria were pregnancy at the time of recruitment, disturbances in understanding or willingness, current polytraumas or coma, or refusal to sign the informed consent. Thirty percent of subjects did not accept to participate; these individuals were generally older and had a higher prevalence of cardiovascular disease (CVD).

The Moli-sani Project was approved by the Catholic University ethics committee. All participants provided written informed consent (baseline and follow-up phases). Moreover, Regional government gave permission and provided us hospital discharge forms and death certificates. Between March 2005 and April 2010, 24,318 subjects were recruited [11,699 men (48.1%), mean age 55.8 years (standard deviation ±12.0), age range 35.0–98.7 years].

Between February and July 2010, we contacted 21,291 participants through telephone interviews: 19,275 (90.5%) accepted to answer, 418 (2.0%) refused, 217 were dead (1.0%) and 1,381 (6.5%) could not be found at home (after three calls in different days).

For the evaluation of seasonal vaccine effectiveness, the whole Moli-sani cohort was eligible. For the evaluation of pandemic vaccine effectiveness, we restricted the study to the sub-cohort of individuals belonging to risk groups defined by the Italian Ministry for Health at the beginning of the pandemic: individuals with chronic respiratory diseases (including asthma), chronic CVD, chronic kidney diseases, hematologic diseases, chronic metabolic disorders including diabetes, cancer, chronic hepatic diseases, congenital and acquired diseases that lead to a reduced antibody production, immune depression (induced by medicine or HIV), chronic inflammatory diseases and syndromes with intestinal malabsorption, diseases associated with an increased risk of inhaling respiratory secretions (e.g., neuromuscular conditions), obesity (MLSPS 2009).

Data collection

Information on the influenza vaccine status and date of administration was obtained from the general practitioners (GP) seasonal vaccine registries and from ASREM (Molise Regional Department of Health) pandemic vaccine registries. An individual was considered protected against pandemic influenza 14 days after receiving the first dose of the pandemic vaccine, similarly after receiving one dose of the 2009–2010 seasonal vaccine.

The following clinical outcomes were considered: ILI, hospitalization for pneumonia, influenza, all respiratory conditions, cardiovascular events and deaths for any cause.

Vaccination, ILI, date of symptoms and outcomes were collected by direct phone interview of participants.

According to the European Union case definition, an ILI episode was identified if the interviewee reported at least one of the following four systemic symptoms: fever or feverishness, malaise, headache, myalgia; and at least one of the following three respiratory symptoms: cough, sore throat, shortness of breath (EC 2009).

Discharge abstract forms were checked to verify hospitalization for all respiratory conditions and for cardiovascular events. The Nominal Registry of causes of death was not available; deaths were recorded by direct interview of a participant's relative. Information on comorbidity, functional status, presence of risk factors was obtained from the baseline database of the Moli-sani project, in addition updated by direct phone interviews and by reviewing hospital discharge abstract forms.

During the recruitment phase (March 2005–April 2010) of the Moli-sani cohort, structured questionnaires were administered by trained investigators to collect personal and clinical information, including socio-economic status, physical activity, medical history, risk factors for CVD and/or cancer, family/personal history for CVD and/or cancer and drug use. Socioeconomic status was defined as a score based on eight variables (income, education, job, housing, ratio between the number of live-in partners and the number of rooms (both current and in childhood) and availability of hot water at home in childhood); the higher the score, the higher the socioeconomic status. Physical activity was assessed by a structured questionnaire and expressed as daily energy expenditure in metabolic equivalent task-hours (Ainsworth et al. 2000). Subjects were classified as non-smokers if they had never smoked cigarettes, ex-smokers if they had smoked cigarettes in the past and had stopped smoking for at least 1 year, and current smokers if they were currently smoking one or more cigarettes per day on a regular basis. Waist and hip circumference, weight and height were measured while the subjects wore no shoes and light underwear. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure was measured by an automatic device (OMRON-HEM-705CP) three times on the non-dominant arm, with the patient lying down for about 5 min. Blood samples were obtained between 7.00 and 9.00 a.m. from participants who had fasted overnight. Serum lipids and blood glucose were assayed by enzymatic reaction methods using an automatic analyzer (ILab-350). Hypertension was defined as systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg or current treatment with antihypertensive drugs in participants with a history of hypertension (Chobanian et al. 2003, Mancia et al. 2007); hypercholesterolemia as total cholesterol $\geq$240 mg/dL or pharmacological treatment to lower blood lipids (ATP-III 2001) and diabetes as fasting glucose level >125 mg/dL or current treatment with anti-diabetic drugs (ADA 2011). Quality of life was assessed by the Italian version 2 of the Short Form Health Survey questionnaire (SF-36), which with only 36 questions yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures (Ware 2000).

Statistical analysis

The frequency of reported ILI in the year before the baseline interview was 25% in non-vaccinated subjects. Fixing alpha at 0.05 and $N = 7{,}760$ (vaccinated subjects out of 25,000 subjects), we calculated a power of 99.9% to detect a reduction in ILI of about 27% (Jefferson et al. 2005) in vaccinated versus non-vaccinated subjects.

The comparison between vaccinated and non-vaccinated subjects considering their characteristics was performed using Chi square test and a multivariable analysis (age–sex adjusted analysis) for categorical variables (procedure CATMOD for SAS), while unpaired t student test and general linear model (age–sex adjusted analysis) were used for continuous variables (procedure GLM for SAS).

The relative risks of events were analyzed by univariable and multivariable Poisson regression analysis with the log link function. Only ILI, hospitalization and deaths occurring between 1 November 2009 and 31 January 2010 were included in the analysis. Subjects who had any episode before November 1st were excluded. Seasonal and pandemic VE against the same outcomes stratified by age groups, risk groups (presence of chronic disease such as CVD, diabetes, pulmonary disease) and period (month) was also estimated.

Baseline information collected at study entry of the Moli-sani project and updated during the present study were used to adjust for potential confounding. Age and gender were always included in multivariable analysis in addition to covariates associated with the outcomes with a $p \leq 0.1$ (pandemic VE analysis) or $p \leq 0.2$ (seasonal VE analysis) in the univariable analysis. We estimated VE as 1 minus the relative risk. Two-sided 95% CI and P values were calculated; $p < 0.05$ was chosen as the level of significance. All analyses were performed using SAS software (version 9.1.3 for Windows, Cary, NC: SAS Institute Inc. 2000–2004).

Results

Pandemic vaccination in the Moli-sani cohort

After checking all ASREM Pandemic Vaccine Registries, 220 subjects from our cohort appeared to be vaccinated against pandemic influenza (in the Molise region, 53,174 doses of pandemic vaccine were available for a total regional resident population of 330,000 inhabitants, but only 2,973 (5.6%) doses were administered). All subjects received the Focetria® vaccine and most of them received one dose of vaccine (206/220, 94%), 14 subjects received two doses.

For this analysis, 8,058 phone interviews were considered, including subjects aged 35–65 years classified as high-risk groups according to the Italian Ministry of Health recommendations.

Table 1 shows the main characteristics of subjects who received pandemic vaccine ($N = 194$, 2.4%) and subjects who did not ($N = 7{,}864$, 97.6%).

Vaccinated subjects were older, more frequently men and vaccinated for 2008 and 2009 seasonal vaccine, with a

Table 1 Characteristics of subjects with and without pandemic vaccine belonging to high-risk group in the Moli-sani cohort ($N = 8{,}058$) (Molise Region, Italy, 2009–2010 flu season)

	Subjects with pandemic vaccine $N = 194$ (2.4%)	Subjects without pandemic vaccine $N = 7{,}864$ (97.6%)	Crude *p* value	Age–sex adjusted *p* value
Sex, male (%)	61.3	49.3	0.001	–
Age, years median (p25–75)	57.0 (50.9–61.2)	54.8 (48.3–60.4)	0.0056	–
High-flu risk (%)	85.0	97.3	<0.0001	<0.0001
Social or health worker (%)	28.9	5.1	<0.0001	<0.0001
Season2009 vaccine (%)	74.7	20.9	<0.0001	<0.0001
Season2008 vaccine (%)	67.5	26.4	<0.0001	<0.0001
Respiratory disease (%)	20.6	9.5	<0.0001	<0.0001
CVD (%)	21.6	5.1	<0.0001	<0.0001
Cancer (%)	10.8	5.5	0.0015	0.0007
Hypertension (%)	59.3	57.2	0.56	0.44
Hypercholesterolemia (%)	39.2	33.2	0.083	0.17
Diabetes (%)	19.1	6.0	<0.0001	<0.0001
BMI, kg/m^2 mean ± SD	29.1 ± 6.1	29.8 ± 5.1	0. 039	0.024
BMI >30 (%)	33.5	50.6	<0.0001	<0.0001
Social status (%)				
Low	28.9	27.1	0.15	0.11
Medium	37.1	43.9		
High	34.0	29.0		
Physical activity (%)				
Low	39.2	34.7	0.21	0.27
Medium	30.4	28.9		
High	30.4	36.4		
Smoking habits (%)				
Yes	23.7	26.1	0.085	0.54
No	41.8	46.5		
Ex	34.5	27.4		
SF-36 mental score, mean ± SD	46.9 ± 10.5	46.9 ± 10.1	0.99	0.61
SF-36 physical score, mean ± SD	43.9 ± 8.1	46.9 ± 5.9	<0.0001	<0.0001
Bathing or dressing yourself (%)[a]				
Yes, limited a lot	10.2	5.2	0.012	0.023
Yes, limited a little	3.9	5.1		
No, not limited at all	85.9	89.7		

BMI body mass index, *CVD* cardiovascular disease, *p25* 25th percentile, *p75* 75th percentile, *SD* standard deviation, *SF-36* short form health survey questionnaire

[a] The following items are about activities you might do during a typical day. "Does your health now limit you in these activities? If so, how much?"

higher prevalence of co-morbidities as compared to non-vaccinated subjects. In particular, the prevalence of CVD, respiratory disease, cancer and diabetes was higher among vaccinated subjects. The SF-36 physical score and functional status ("bathing or dressing yourself") were lower in vaccinated subjects. BMI (also considering obesity as BMI >30) was higher in non-vaccinated subjects. However, there were no differences in social status, physical activity and smoking habits between vaccinated and non-vaccinated subjects.

Subjects at high risk without pandemic vaccine answered that they refused to be vaccinated since they consider themselves not at high risk (33.9%), or their GP suggested them not to vaccinate (3.0%) or they were fear of side effects and doubted about vaccine efficacy (8.5%); 14% preferred to receive only the seasonal vaccine and 40% answered "other".

Pandemic vaccine effectiveness

After the exclusion of subjects who had an episode of ILI before November 1st, the final analysis was performed on 7,868 subjects. Twelve cases of ILI (6.7%) among vaccinated subjects and 606 (7.9%) among non-vaccinated subjects were reported (Table 2). In multivariable analyses (adjusted for age, sex, respiratory disease, season 2008 vaccine and month) the pandemic VE was 3% (95% CI: −50, 38).

There were seven cases of hospitalizations for respiratory conditions in the target group for pandemic vaccination.

Table 2 ILI by EU case definition incidence and relative risks for ILI in pandemic vaccinated and non-vaccinated subjects aged 35–65 years and belonging to high-risk group in the Moli-sani cohort (*N* = 7,868) (Molise Region, Italy, 2009–2010 flu season)

	Subjects with pandemic vaccine *N*: 180 (2.3%)	Subjects without pandemic vaccine *N*: 7,688 (97.7%)	Univariable RR (95% CI)	*P* value	Multivariable RR (95% CI)	*P* value
Subjects without ILI	168	7,082	–		–	
Subjects with ILI	12	606	0.84 (0.49–1.47)	0.55	0.97 (0.62–1.50)	0.88
Incidence of ILI	6.7%	7.9%				

Multivariable analysis adjusted for age, sex, respiratory disease and season2008 vaccine and month

95% CI 95% confidence interval, *EU* European Union, *ILI* influenza-like illness, *RR* relative risk

When the whole Moli-sani cohort was analyzed only 13 subjects were hospitalized, all of them were not vaccinated for pandemic influenza. Similarly, 14 hospitalizations for CVD in the target group for pandemic vaccination were found and when the whole Moli-sani cohort was considered, 33 subjects were hospitalized for CVD, but none of them was vaccinated. In the sub-cohort of subjects at high risk, between 1 November 2009 and 31 January 2010, two subjects died, neither having received pandemic vaccination.

Seasonal vaccination in the Moli-sani cohort

Out of 19,275 phone interviews, 19,222 were considered reliable. To validate the vaccination status of subjects, phone interview was cross-linked to GP Seasonal Vaccine Registries: for 2,168 subjects the cross-validation of seasonal vaccine status was incongruent and for 377 subjects the vaccination date was not available from GP registries. After exclusion of these subjects, the descriptive analysis on cross validated data was performed on 16,677 subjects.

Seasonal vaccine was received by 26.6% ($N = 4{,}441$) of the whole population. The coverage of seasonal vaccine in elderly subjects (age $\geq$65 years) was 63%, while in middle-aged subjects at high-flu risk was 21.9%.

Table 3 shows the main characteristics of vaccinated and non-vaccinated subjects. Vaccinated subjects were older, more frequently men and vaccinated for pandemic and season 2008 vaccine, with a higher prevalence of co-morbidities as compared to non-vaccinated subjects, while SF-36 physical and SF-36 mental score and the functional status were lower. The prevalence of former smokers was higher in the vaccinated group (34.4% vs. 23.9%), while current smokers were more prevalent in the non-vaccinated group. There was no difference in social status distribution.

Seasonal vaccine effectiveness

After the exclusion of subjects who had an episode of ILI before November 1st, the final analysis was performed on 16,212 subjects. We recorded 262 (6.1%) ILI in vaccinated and 792 (6.6%) in non-vaccinated subjects (Table 4). In multivariable analysis, after adjusting for age, sex, respiratory disease, hypertension, SF-36 mental score and month, there was no significant association between seasonal vaccine and ILI [VE: −12% (95% CI: −26, 1)].

For the age group 35–65 years the adjusted RR was 1.17 (95% CI: 1.01–1.35) (VE: −17% (95% CI: −35, −1), for the age group $\geq$65 years the adjusted RR was 0.92 (95% CI: 0.63–1.36) (VE: 8% (95% CI: −36, 37) and for people belonging to high-risk groups and aged 35–65 years the adjusted RR was 1.17 (95% CI: 0.98–1.39) (VE: −17% (95% CI: −39, 2) (Table 4).

Table 5 shows incidences and adjusted relative risks (adjusted for age, sex, respiratory disease, season 2008 vaccine) for ILI, stratified by month of study. Seasonal vaccine was significantly protective for ILI only in November.

In the whole Moli-sani cohort, we found 11 hospitalizations for respiratory events [6 (0.14%) were vaccinated and 5 (0.05%) non-vaccinated ($p = 0.07$, adjusted for age and gender)] and 26 hospitalizations for CVD [15 (0.34%) were vaccinated and 11 (0.1%) non-vaccinated ($p = 0.002$, adjusted for age and gender)].

Between 1 November 2009 and 31 January 2010, six subjects died and the incidence of death was 0.04% [4 (0.08%) in vaccinated and 2 (0.02%) in non-vaccinated subjects].

Since the numbers of events were quite low, we did not perform multivariable adjusted analysis for all these outcomes.

Discussion

Vaccine coverage

Information on the influenza vaccine coverage in our study was obtained from public vaccine registries and cross-checked with direct report from interviewed subjects. In the target group (subjects at high-flu risk and aged 35–65 years) of the Moli-sani cohort, the pandemic vaccine coverage was very low, namely 2.4%. In Italy, the vaccine coverage calculated on the doses administered and

Table 3 Characteristics of subjects with and without seasonal vaccine in the Moli-sani cohort ($N = 16{,}677$) (Molise Region, Italy, 2009–2010 flu season)

	Subjects with seasonal vaccine $N = 4{,}441$ (26.6%)	Subjects without seasonal vaccine $N = 12{,}236$ (73.4%)	Crude *p* value	Age–sex adjusted *p* value
Sex, male (%)	50.4	46.8	<0.0001	–
Age, years median (p25–75)	67.5 (59.9–74.1)	52.8 (46.3–60.3)	<0.0001	–
Age 35–65 years (%)	44.6	88.2	<0.0001	–
Pandemic vaccine (%)	2.2	0.4	<0.0001	<0.0001
Season2008 vaccine (%)	89.7	3.5	<0.0001	<0.0001
Respiratory disease	13.5	3.7	<0.0001	<0.0001
CVD (%)	14.7	2.6	<0.0001	<0.0001
Cancer (%)	6.7	3.0	<0.0001	<0.0001
Hypertension (%)	76.8	47.6	<0.0001	<0.0001
Hypercholesterolemia (%)	39.2	29.2	<0.0001	<0.0001
Diabetes (%)	11.4	2.6	<0.0001	<0.0001
BMI, Kg/m^2 mean ± SD	29.0 ± 4.9	27.8 ± 4.7	<0.0001	<0.0001
BMI >30 (%)	37.0	27.9	<0.0001	<0.0001
Social status (%)				
Low	36.3	25.2	<0.0001	0.10
Medium	42.6	43.5		
High	21.1	31.3		
Physical activity (%)				
Low	31.3	33.9	<0.0001	0.048
Medium	41.4	29.5		
High	27.3	36.6		
Smoking habits (%)				
Yes	15.3	26.9	<0.0001	<0.0001
No	50.3	49.2		
Ex	34.4	23.9		
SF-36 mental score, mean ± SD	45.9 ± 10.3	47.2 ± 9.8	<0.0001	0.0009
SF-36 physical score, mean ± SD	44.3 ± 7.1	47.8 ± 5.7	<0.0001	<0.0001
Bathing or dressing yourself (%)[a]				
Yes, limited a lot	9.7	4.5	<0.0001	<0.0001
Yes, limited a little	9.6	4.0		
No, not limited at all	80.7	91.5		

BMI body mass index, *CVD* cardiovascular disease, *p25* 25th percentile, *p75* 75th percentile, *SD* standard deviation, *SF-36* Short Form Health Survey questionnaire

[a] The following items are about activities you might do during a typical day. “Does your health now limit you in these activities? If so, how much?”

population eligible for vaccination was 4.3%, nevertheless Italy has been the first European country to initiate the vaccination for the pandemic influenza (Rizzo et al. 2010a, b). The national coverage in the target group was quite similar to those calculated in our population where children and pregnant women were not included. In a Greek study based on general medical data, the vaccination rate was 12% overall (Rachiotis et al. 2010), while in Spain it was overall 23.6% in a study based on doses administered (Pérez-Rubio et al. 2010) and 14.6% in a study taking as the data source nominal vaccination registers in public and private centers (Jiménez-García et al. 2011). These low coverage rates were specific for the pandemic vaccine, since the coverage for seasonal vaccine, especially in elderly, was as expected from previous year both in our population [63% of elderly (age ≥65 years) of our cohort received seasonal vaccine] in Italy [66% of vaccine coverage in elderly (Ministero della salute 2011)] and in other European countries (Valenciano et al. 2011).

In a recent study (Ferrante et al. 2011), PASSI (Progressi delle Aziende Sanitarie per la Salute in Italia) surveillance described perceptions, knowledge, attitudes and behaviors of the population regarding the pandemic A(H1N1) influenza. Among those who had not been vaccinated yet and who thought they had not yet had influenza, the proportion of people who would accept the pandemic vaccine was 22% (population at risk affected by chronic diseases: 29%). One of the hypotheses, indeed, suggested to explain such low coverage rates is that the vaccination campaign started closely to the peak of the epidemic curve in Italy. In particular, some people’s perceptions “indicators” (perception of high risk of catching the A(H1N1) flu,

Table 4 ILI by EU case definition incidence and relative risks for ILI in seasonal vaccinated and non-vaccinated subjects in Moli-sani cohort (*N* 16,212) (Molise Region, Italy, 2009–2010 flu season)

	Subjects with seasonal vaccine	Subjects without seasonal vaccine	Univariable RR (95% CI)	*P* value	Multivariable RR (95% CI)	*P* value
Whole cohort[a]	4,285 (26.4%)	11,927 (73.6%)				
Subjects without ILI	4,023	11,135	–		–	
Subjects with ILI	262	792	0.92 (0.80–1.05)	0.23	1.12 (0.99–1.26)	0.06
Incidence of ILI	6.1%	6.6%				
Age 35–65 years[b]	1,894 (15.3%)	10,510 (84.7%)				
Subjects without ILI	1,768	9,793	–		–	
Subjects with ILI	126	717	0.97 (0.81–1.17)	0.79	1.17 (1.01–1.35)	0.04
Incidence of ILI	6.6%	6.8%				
Age ≥65 years[c]	2,391 (62.8%)	1,417 (37.2%)				
Subjects without ILI	2,255	1,342	–		–	
Subjects with ILI	136	75	1.07 (0.82–1.41)	0.61	0.92 (0.63–1.36)	0.70
Incidence of ILI	5.7%	5.3%				
Age 35–65 years and at high flu risk[d]	1,392 (20.5%)	5,390 (79.5%)				
Subjects without ILI	1,295	4,987	–		–	
Subjects with ILI	97	403	0.93 (0.75–1.15)	0.52	1.17 (0.98–1.39)	0.08
Incidence of ILI	7.0%	7.5%				

95% CI 95% confidence interval, *EU* European Union, *ILI* influenza-like illness, *RR* relative risk

[a] Multivariable analysis adjusted for age, sex, respiratory disease, hypertension, SF-36 mental score and month

[b] Multivariable analysis adjusted for age, sex, respiratory disease, SF-36 mental score and month

[c] Multivariable analysis adjusted for age, sex, respiratory disease, season2008 vaccine, hypercholesterolemia, SF-36 mental score and month

[d] Multivariable analysis adjusted for age, sex, respiratory disease, hypertension, obesity (BMI >30), smoking habits and month

Table 5 Adjusted relative risks in seasonal vaccinated against non-vaccinated subjects by month of study (November, December, January) (Molise Region, Italy, 2009–2010 flu season)

	ILI incidence in subjects with seasonal vaccine (%)	ILI incidence in subjects without seasonal vaccine (%)	Univariable RR (95% CI)	*P* value	Multivariable RR (95% CI)	*P* value
November	0.6	1.7	0.30 (0.20–0.47)	<0.0001	0.49 (0.30–0.78)	0.003
December	1.9	2.0	0.94 (0.73–1.20)	0.62	1.20 (0.90–1.60)	0.22
January	3.8	3.1	1.24 (1.03–1.49)	0.024	1.21 (0.98–1.51)	0.08

Multivariable analysis adjusted for age, sex, respiratory disease, hypertension and SF-36 mental score and month

95% CI 95% confidence interval, *ILI* influenza-like illness, *RR* relative risk

worrying about the pandemic, limitation of outdoor activities, willingness to accept vaccination) were highest in the first two-week period of pandemic surveillance and then followed a progressive decline. As a consequence, even when the spread of the disease reached its maximum level, just one-third of the adult population would agree to be vaccinated and this proportion showed a further decline later on (Ferrante et al. 2011). The majority of non-vaccinated target subjects of our cohort reported that they refused to be vaccinated since they consider themselves not at high risk (33.9%) or because they preferred to receive only the seasonal vaccine (14%). Of interest, 8.5% of the population reported that they were scared about side effects and doubted about vaccine efficacy and 3% reported that their GP suggested them not to be vaccinated. Considering the PASSI study (Ferrante et al. 2011), 81% of respondents considered GPs the most reliable source of information, which people would contact in case of need. In this context the greatest effort should be put in GP information and education. Indeed GPs should know exactly how to deal with their patients, providing optimal management for patients and empowering patient self care. GPs should be prompt in detecting and monitoring epidemics of viral illnesses in the community, thus public health measures would be more effective with close collaboration between public health authorities and GPs (Lee and Chuh 2010).

The answers obtained in our study were similar to those obtained in other countries and raise serious concern on which kind of information has really reached not only the general population but also health providers. Indeed, despite the extensive information campaign launched by the central government and regional authorities, several negative messages also reached the population (Lambert 2010; Poland 2011). Moreover, a number of target subjects considered themselves not at risk. This suggests that awareness of disease is still low among general population (Costanzo et al. 2008) and extension of vaccination indication to the whole population could have given better results in terms of coverage (Jiménez-García et al. 2011).

The major factors associated with vaccination were similar for both pandemic and seasonal vaccine: older age, male sex, having been vaccinated in previous seasons, high presences of the major co-morbidities and low level of physical functional status. These results were similar to those obtained in other studies (Jiménez-García et al. 2011).

Vaccine effectiveness

Our study shows a non significant pandemic vaccine efficacy of 3% (95% CI: −50, 38). There were few cases of hospitalization and death in our cohort, all in non-vaccinated subjects. Due to the low actual coverage of pandemic vaccine as compared to the expected, our study had no sufficient statistical power to detect a reliable estimate of vaccine efficacy. Several studies have reported high effectiveness of pandemic vaccine in preventing influenza A (H1N1) and most of these studies considered as outcome ILI confirmed by test laboratory (Hardelid et al. 2011; Puig-Barberà et al. 2010; Pelat et al. 2011; Valenciano et al. 2011; Wichmann et al. 2010; Vaux et al. 2011).

Epidemiological estimations of our study of seasonal VE are low or without effect as it could have been expected, given the failed match between the vaccines and the circulating strain. In particular, for the two groups, subjects aged 35–65 years and people belonging to high-risk groups always aged 35–65 years, the VE against ILI by EU case definition was −17% (95% CI:−35, −1% and −39, 2%, respectively). It seems that seasonal vaccine increased the risk of both ILI and ARI in middle-age and in subjects at flu-risk, although a recall bias, by which vaccinated individuals were more likely to remember any event correlated to vaccine failure, cannot be excluded. No association between seasonal vaccine and ILI in people aged >65 years was observed. Stratified analysis by month showed that the seasonal vaccine was effective in the first month of administration, during the period of peak of influenza.

European published studies on the possible effectiveness of seasonal influenza vaccination against ILI (without and with laboratory test confirmation) have shown controversial conclusions: some did not find any association (Puig-Barberà et al. 2010; Hardelid et al. 2011; Valenciano et al. 2011), while others found a statistically significant effectiveness in preventing ILI (Pelat et al. 2011).

Analysis of VE against hospitalization for respiratory or CVD that is usually associated with influenza did not show any significant protective effect of seasonal vaccine in individuals at high-risk group (VE: 77%, 95% CI: −1, 95%). About this risk category few recent data are available, while in the elderly, vaccination against influenza appears to be associated with reductions in the risk of hospitalization for CVD and pneumonia or influenza as well as the risk of death from all causes during influenza seasons (Jefferson et al. 2005).

The majority of studies on vaccine efficacy are observational. Randomized controlled trials are not feasible because of ethical and economic reasons, and other constraints. In this context, the main weakness of observational studies is the absence of random assignment of vaccine to study subjects (Rothman 2002). It is necessary to quantify the potential magnitude of common potential measured confounders and their relative contribution to avoid inconsistent conclusions (Rothman 2002; Mori et al. 2008).

Among observational studies, the cohort study is the elective study to be carried out for evaluation of VE. The study design of a cohort study, indeed, allows to better classify subjects as vaccinated/unvaccinated, to measure more covariates (confounding or effect modification factors) and multiple outcomes (primary and secondary outcomes), to eliminate recall bias in comparison with the case-control design.

The strength of the present study is that all the analyses have been adjusted by age, sex, and taking in account of all potential confounding factors. However, this study has demonstrated that even with a large cohort the estimation of VE is made difficult in the absence of specific outcomes (i.e., laboratory confirmed outputs) and with a very low coverage of vaccination.

Limitations of the study

In the Molise region, during 2009–2010 pandemic influenza season, hospitalized people only were nasopharyngeal swabbed to confirm the occurrence of pandemic influenza A(H1N1). Only six swabs from patients belonging to our cohort were taken, of which two tested positive for A(H1N1) virus. Our estimates are, therefore, entirely based on clinical outcomes, with lower specificity than laboratory confirmed outcomes. Moreover, ILI is available as outcome from subject interview, therefore, we cannot exclude some sort of recall bias by which individuals who were vaccinated were also more likely to remember any event that they can attribute to vaccine failure.

In addition the coverage of pandemic vaccination was very low and consequently the power of our study to detect the pandemic VE decreased.

Our cohort, randomly recruited form the general population, only included subjects older than 35 years of age; therefore, the results obtained cannot be extended to the whole population.

In conclusion, during the 2009–2010 influenza season, the coverage of pandemic vaccine was very low in a Southern Italy population, with no protective effect against ILI. Great effort should be put in information and education on this issue. Public health measures should be more effective, improving the close collaboration between public health authorities, GPs and target population.

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Appendix: Moli-Sani project investigators

Chairperson: Licia Iacoviello

Steering Committee: Maria Benedetta Donati and Giovanni de Gaetano (Chairpersons), Simona Giampaoli (Istituto Superiore di Sanità, Roma).

Bio-ethics Committee: Jos Vermylen (University of Leuven, Belgio), Chairman, Ignacio De Paula Carrasco (Pontificia Academia Pro Vita, Roma).

Event adjudicating Committee: Deodato Assanelli (Università di Brescia), Francesco Alessandrini (UCSC, Campobasso), Vincenzo Centritto (Campobasso), Paola Muti (Istituto Nazionale Tumori Regina Elena IRCCS, Roma), Holger Schunemann (McMaster University Health Sciences Centre, Canada), Pasquale Spagnuolo (Ospedale San Timoteo, Termoli), Dante Staniscia (Ospedale San Timoteo, Termoli), Sergio Storti (UCSC, Campobasso).

Scientific and Organizing Secretariat: Francesco Zito (Coordinator), Americo Bonanni, Chiara Cerletti, Amalia De Curtis, Augusto Di Castelnuovo, Licia Iacoviello, Antonio Mascioli, Marco Olivieri.

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Informatics: Marco Olivieri (Coordinator), Maurizio Giacci, Antonella Padulo (till September 2008), Dario Petraroia (till September 2007).

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