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ORIGINAL RESEARCH



Effectiveness of the trivalent MF59 adjuvated influenza vaccine in preventing hospitalization due to influenza B and A(H1N1)pdm09 viruses in the elderly in Italy, 2017 – 2018 season

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ABSTRACT

Background: Evidence on influenza vaccine effectiveness (VE) in preventing mortality and morbidity in the elderly is weak. Our aim was to measure the VE against severe outcomes in the elderly.

Methods: We conducted a multicentre hospital-based test-negative design (TND) case-control study, during the 2017/18 season, in four Italian hospitals. The study population included individuals aged ≥ 65 years hospitalized with Severe Acute Respiratory Infections (SARI). Patients were classified as cases and controls based on the results of the PCR influenza testing. We estimated VE by virus subtypes and specific VE for the trivalent adjuvanted vaccine (TIVadj).

Results: 502 patients with SARI were enrolled: 118 (23.5%) tested positive (cases) and 384 (76.5%) tested negative (controls) for influenza. The adjusted VE of 48.5% for all vaccines was comparable to the adjusted VE for the TIVadj vaccine (48.3%). Adjusted VE for the TIVadj vaccine was 67.5% for A(H1N1)pdm09 and 44.5% for B viruses.

Conclusion: We show a moderate adjusted VE of the TIVadj against all viruses, a good adjusted VE against A(H1N1)pdm09 strains and a moderate adjusted VE against B strains, despite a mismatch between the B circulating lineage and the lineage included in the vaccine. This is likely due to the cross-protection among B strains induced by the TIVadj in elderly patients.

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Influenza vaccine effectiveness; influenza trivalent vaccines; TIVadj; elderly; hospitalized SARI cases

1. Introduction

Influenza is a serious public health problem and a significant source of direct and indirect costs, for the implementation of control measures, and for the management of cases and complications of the disease [1,2]. The vaccine composition varies from year to year, based on an early identification of circulating virus strains during the northern hemisphere winter and during the summer in the southern hemisphere.

The Italian Ministry of Health publishes yearly recommendations for influenza prevention with a focus on vaccination, which is recommended and provided free of charge to elderly individuals (≥ 65 years), people with comorbidities, pregnant women and health care workers [3]. Vaccines are provided by general practitioners (GPs) and local vaccine units. The vaccination program generally starts in mid October. In 2017–18, in Italy the vaccine coverage was 15.3% in all ages and 52.7% among the elderly [4]. In Italy, the overall influenza vaccine coverage has been decreasing in the past few years, mainly due to the pandemic vaccine campaign and issues related to the TIVadj vaccine batches recall in 2012/2013 and 2014–15 seasons. Flu vaccination coverage has been slightly increasing

from 2015–16, but still remains below the WHO minimum target (75%) [4]. In Italy, the 2017–18 influenza season was characterised by a very high incidence and the circulation of the viruses A/H1N1 and B/Yamagata. In all Italian regions, the Influenza-like-illness (ILI) incidence exceeded the moving epidemic method (MEM) threshold on the 49th week of 2017 (ISO week 49–2017), which was earlier compared to the previous seasons, during which the MEM threshold was exceeded, usually in the 52nd week of the year (excluding the pandemic 2009/2010 season) [5].

Influenza vaccines have been shown to be effective in preventing influenza infection in healthy adults, but weak evidences have been gathered to prove their effectiveness in preventing influenza-related mortality and morbidity in the elderly [6,7]. Several reviews [8] classified as 'moderate to poor' the evidences regarding influenza vaccine effectiveness (VE) in this target group [9]. Among the elderly, for whom a reduced capacity to produce antibodies leads to an impaired immune response (also known as immune-senescence) [10], the evidence gathered in a 2018 Cochrane review suggested a modest VE of the trivalent inactivated vaccines (TIV) [11]. However, on the other hand,

Article highlights

- Influenza adjusted vaccine effectiveness in elderly, community-dwelling patients hospitalised for Severe Acute Respiratory Infections was moderate for all vaccines (48.5%).
- As 94% of the vaccinated individuals included in our population had received the trivalent adjuvanted vaccine (TIVadj), we could calculate brand-specific figures.
- TIVadj showed a moderate adjusted VE against all viruses (48.3%); a good adjusted VE against A(H1N1)pdm09 strains (67.5%); a moderate adjusted VE against B viruses (44.5%)
- The moderate VE against B viruses, despite the lineage mismatch between the circulating strains and the strains included in the vaccine can be explained by the typical cross-lineage protection induced by the TIVadj in elderly patients.

several studies have shown a reduction in hospitalization (for pneumonia and influenza) and deaths, during the influenza season (aOR 0.86, 95% CI 0.79–0.92) [12] and a significant reduction in the risk of hospitalization due to laboratory-confirmed influenza among adults aged ≥ 50 years of age, regardless of age group [13]. In another study on older individuals, vaccination was 58% effective in preventing medically attended laboratory-confirmed influenza in adults ≥ 50 years of age, as well as in adults ≥ 65 years of age [14].

In Italy, the MF59[™] adjuvanted influenza vaccine is available since 1997 [9]. The MF59[™] adjuvanted influenza vaccine is now approved in more than 30 countries, including the US, with an estimate of 81 million doses distributed worldwide until 2017 [15]. This vaccine seems to have an effect in enhancing the immune response in the elderly and in subjects with underlying chronic disease, compared with non-adjuvanted vaccines [16,17]. However, to date, the number of articles trying to address the vaccine effectiveness of the MF59[™] adjuvanted influenza vaccine in the elderly is low [18].

In order to measure the vaccine effectiveness (VE) against severe outcomes and to broadly capture a population belonging to the target group for the influenza vaccination, hospital based studies, using laboratory confirmed influenza hospitalisation as an outcome, have been widely used.

In this article, we conducted a multicentre case-control study using a test-negative design in 4 hospitals located in Italy representative of the Northern (Genova) Center (Siena, Roma), and Southern Italy (Bari). Since 94% of the vaccinated individuals included in our sample were vaccinated with the MF59 adjuvanted vaccine, we were able to estimate brand-specific VE for the TIVadj (R) vaccine.

2. Methods

This is a multicentre hospital-based test-negative design (TND) case-control study, conducted between week 50–2017 and week 17–2018 in four Italian hospitals, namely the Department of Biomedical science and medical Oncology of the University of Bari, Puglia Region; the Department of Physiopathology, Experimental Medicine and Public Health, University of Siena, Tuscany Region; the IRCCS University Hospital San Martino, Genoa, Liguria Region; the Department of Medical-Surgical Sciences and Translational Medicine,

University of Rome ‘Sapienza’, Lazio Region. The four participating hospitals are academic hospitals, with 600 to over 1,000 beds. Study sites adapted to their local settings a generic study protocol developed within the IMOVE+ EU funded Project [19–21].

2.1. Study population

The study population included all community-dwelling individuals aged ≥ 65 years, hospitalised between week 47–2017 (20–26 November 2017) and week 15–2018 (9–15 April 2018), with a clinical picture of Severe Acute Respiratory Infections (SARI). All individuals belonged to the target group for influenza vaccination, due to their age.

Exclusion criteria were: age < 65 years at the time of admission; presence of contraindications for influenza vaccination; discharge from a previous hospital within 48 hours from symptom onset; SARI cases with a previous laboratory-confirmed influenza during the same season; patients refusing to participate or unable to give consent; patients who had received antiviral drugs before swabbing.

2.2. Study procedures

In each participating hospital, a study coordinator followed standard operational procedures defined among the study sites. At least one medical doctor, together with medical residents or nurses, were in charge of checking for eligible hospitalised patients daily. Eligible patients were interviewed by researchers, after signing an informed consent. Informed consent was collected from patients’ relatives in case the patient was not able to sign the consent.

After the informed consent was signed, a questionnaire was administered to the patients or to their relatives. The following data were collected through the questionnaire: date of symptom onset, symptoms, presence of chronic underlying diseases, frailty, influenza vaccination history (for the current season and for the two past seasons), pneumococcal vaccination history (PCV and/or PPSV), laboratory results.

Enrolled patients’ GPs were contacted by telephone, for confirming vaccination status and collecting vaccine dates and brands.

Subsequently, data were entered on a dedicated web-based system, characterized by warning and blocking procedures to improve the quality of data entry. Data were checked weekly for consistency and completeness, with specific Stata do- files at the national level. In case of inconsistency and of missing values, regular bi-weekly feedback was sent to the hospital coordinator.

2.3. Case definitions

We applied the SARI case definitions of the IMOVE+ EU funded Project [19–21]. Briefly, a SARI patient was defined as an hospitalised individual with at least one systemic symptom or sign (fever or feverishness, malaise, headache or myalgia) OR deterioration of general conditions OR deterioration of functional status AND at least one respiratory symptom or sign (cough, sore throat or shortness of breath), at admission

or within 48 hours from admission. Only cases with an onset less than 7 days before admission were considered.

A case of confirmed influenza was a SARI patient who was swabbed and tested positive for any influenza virus, using real-time polymerase chain reaction (RT-PCR).

Controls were SARI patients who tested negative for any influenza virus using RT-PCR.

2.4. Laboratory confirmation

Influenza laboratory confirmation was performed using RT-PCR. The laboratory was located inside each of the participating hospital. Isolates underwent a molecular analysis for currently circulating influenza viruses. A systematic subset underwent gene sequencing and was sent to the National Reference Centre.

2.5. Sample size

Assuming a vaccination coverage of 50% among the source population and a proportion of patients testing positive for influenza of 30% among swabbed SARI patients, a total sample of 516 SARI patients, of which 155 testing positive (cases) and 361 testing negative (controls) for influenza, was considered sufficient to detect an OR of 0.4 (=VE of 60%) with a power of 80% and a precision of 20%.

2.6. Statistical analysis

We excluded from the analysis patients swabbed more than 7 days after symptom onset; patients with missing laboratory results; patients with missing information on vaccination status; those vaccinated < 14 days before symptom onset; influenza A cases who were not subtyped; and controls with symptom onset before the first confirmed case.

We compared cases (all viruses, A(H1N1)pdm09 and B) and controls using Chi-square test or Fisher exact test for categorical variables and t-test or Mann-Whitney test for continuous variables.

The vaccine effectiveness (VE) was computed as $1 - \text{Odds Ratio (OR)}$ and 95% confidence interval (95%CI) was computed around the point estimate.

We estimated VE for all influenza virus subtypes, for A (H1N1)pdm09 and B, as no A/H3N2 cases were reported in the study population. Moreover, we also estimated VE by vaccine type (all vaccines type, TIVadj).

Using a multivariable logistic regression model we calculated VE adjusting for confounding factors: symptom onset date, age, sex, presence of at least one chronic condition, current influenza vaccination, former influenza vaccination (previous two seasons), and number of hospital visits. The symptom onset date was modelled as a restricted cubic spline with 3 knots.

All statistical analyses were carried out using Stata version 11.2 (StataCorp, College Station, Texas).

2.7. Ethical approval and consent

The study was approved by the Ethical Committee of the Istituto Superiore di Sanità (ISS), Rome, Italy (Prot. PRE 553/17–18 July 2017). Written informed consent was obtained for all of the included patients.

3. Results

Figure 1 shows the geographic distribution of the four participating hospitals (Genoa, Siena, Bari and Rome). In the study period, 525 patients with SARI were recruited in the study and swabbed in the participating hospitals: 209 patients (39.8%) were enrolled at the Bari hospital, 188 (35.8%) at the Genoa hospital, 111 (21.2%) at the Rome hospital and 17 patients (3.2%) at the Siena hospital.

Twenty-three patients were excluded from the analysis for different reasons (Figure 2). Eleven cases were excluded due to missing information on vaccination status or on date of vaccination. The first influenza case recruited in the study, was confirmed on the 10th of December 2017 (49–2017 ISO week), therefore, ten controls recruited with symptom onset before the first confirmed case were excluded from the analysis. Moreover, as the last SARI case recruited in the study was confirmed on 1 April 2018 (13–2018 ISO week), 2 controls recruited with symptom onset after this date were excluded from the analysis. Nine cases were excluded as more than 7 days had passed between the onset date and the swab date. One case was excluded as he or she showed symptoms within 15 days from the vaccination date.

Therefore, a total of 502 patients with SARI were included in the analysis. Of these, 118 (23.5%) tested positive and 384 (76.5%) tested negative for influenza. Among all the patients with a positive swab, 91 cases were influenza B, 23 were influenza A(H1N1)pdm09, 1 case was influenza A(H3N2), 1 case was a non-subtyped influenza A and 2 cases had a coinfection with 2 influenza viruses (A(H1N1)pdm09 + A(H3N2) and A(H1N1)pdm09 + B) (Figure 2).

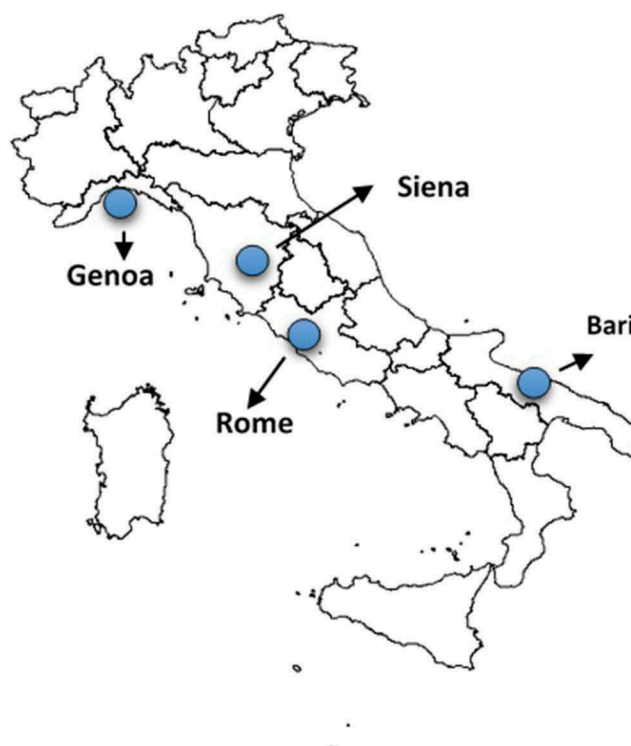


Figure 1. Geographical distribution of participating hospitals.

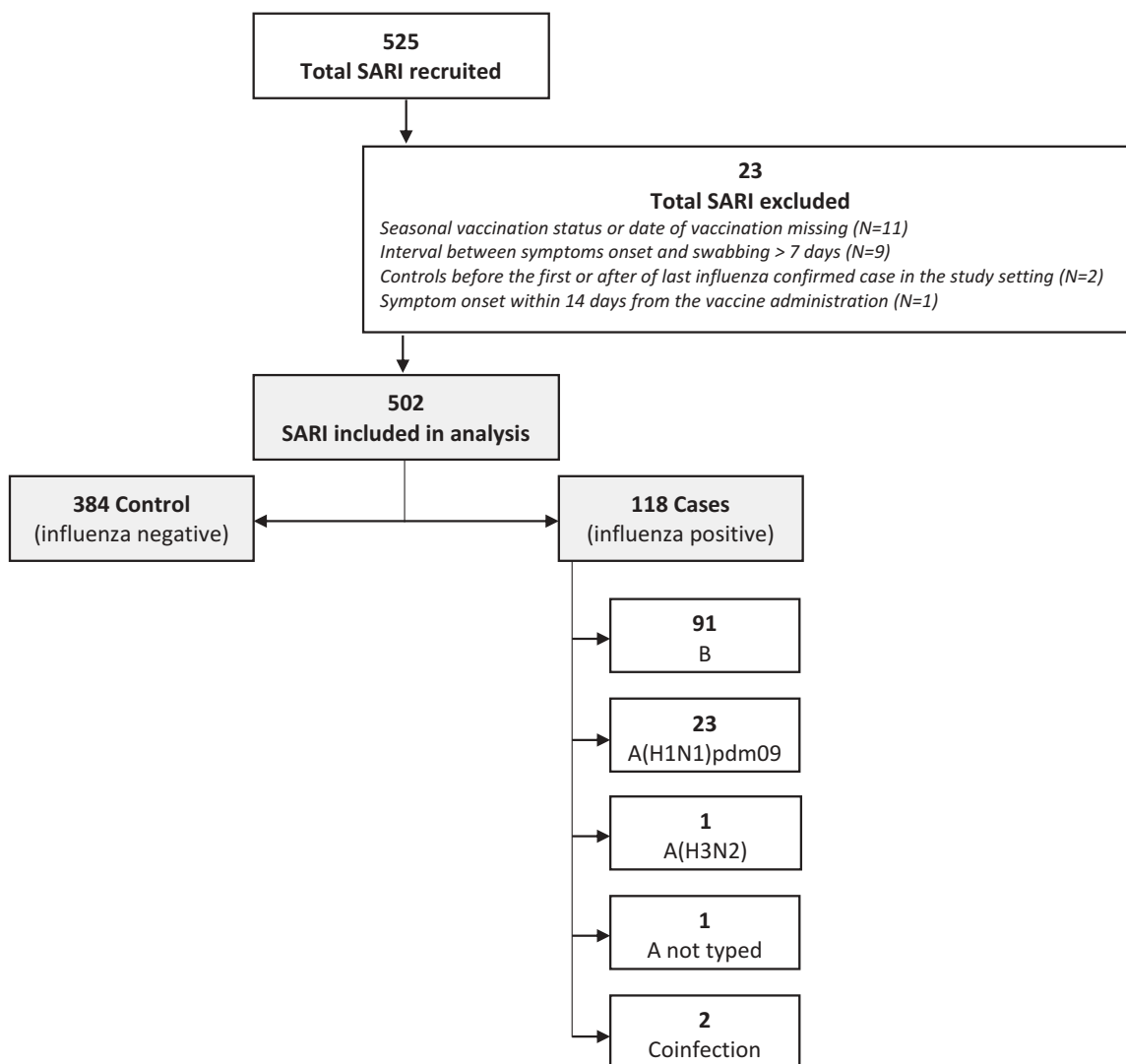


Figure 2. Flowchart of number SARI inclusion and exclusion criteria, I-MOVE+ case-control study, Italy, 2017–18.

Most SARI cases (130, 26%) were recruited during the first two weeks of 2018. The highest number of SARI cases were observed on week 02–2018 (Figure 3).

We report a comparison between cases (any influenza virus) and controls (Table 1), between influenza B cases and controls (Table 2), and between A(H1N1)pdm09 confirmed cases and controls (Table 3). We decided not to report information for A(H3N2) and untyped A influenza cases, due to the low number of cases caused by these two subtypes. In our sample, cases and controls were similar for most demographic characteristics, underlying conditions and vaccine status (Tables 1 and 2).

3.1. Vaccination against seasonal influenza 2017–18

A total of 250 SARI patients (43 cases and 207 controls) received the seasonal influenza vaccine in the 2017–18 season. The first vaccination was administered on week 41–2017 (10 October 2017) and the last was administered on week 52–2017 (29 December 2017). In our sample, seasonal influenza vaccine coverage was 49.8%. Among patients aged

<80 years the coverage was 44.3%, and among those aged ≥80 years it was 59.1% (p-value = 0.021) (Table 4). For seven vaccinees, information on vaccine brand was missing. The list of vaccine administered to the study population is reported in Table 5, 94% of the vaccinees received the MF59 adjuvanted vaccine.

3.2. Crude and adjusted vaccine effectiveness in preventing influenza infection

The VE was estimated for all viruses and for A(H1N1) and B virus by all vaccines and by TIVadj (Figure 4). The crude VE estimate for all vaccines and against all influenza viruses was 51.0% (95%CI: 25.0 to 68.0). After adjusting by age group and time from onset to swab, the VE estimate was 48.5% (95%CI: 20.0 to 66.9). The crude VE estimates against A(H1N1)pdm09 was 70.5% (95%CI: 23.4 to 88.6) and after adjusting by age group, the VE estimate was 65.1% (95%CI: 8.2 to 86.7). The crude vaccine effectiveness against B influenza viruses was 51.5% (95%CI: 23.4 to 88.6) and after adjusting by age group and time from onset to swab, the VE estimate was 46.8% (95%CI: 13.2 to 67.4).

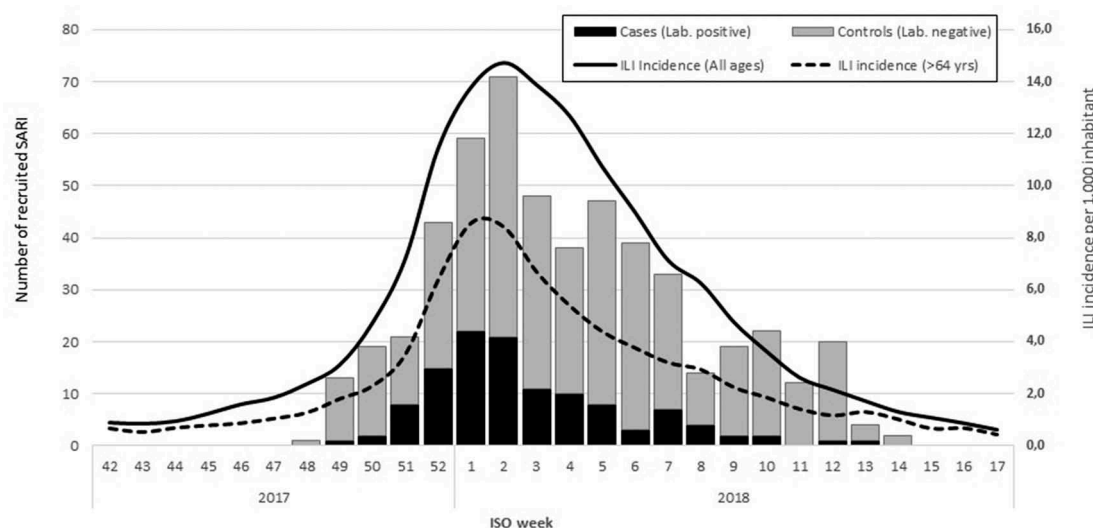


Figure 3. Number of recruited SARI by week of onset, I-MOVE+ case-control study, Italy, 2017–18.

Table 1. Comparison between test-positive for all viruses 'Cases' (N = 118) and test-negative 'Controls' (N = 384) SARI recruited cases at hospital level. I-MOVE+ hospital study (N = 502): Italy, 2017–18 season.

	All Cases (N = 118)	Controls (N = 384)	p-value
	N (%)	N (%)	
Mean age	76.3	77.8	0.044
Aged 65–79 years	82 (69.5)	234 (60.9)	0.092
Sex = male	68 (57.6)	229 (59.6)	0.698
Average number of hospitalisation in past 12 months	0.4	0.7	0.053
Average number of GP visits in past 12 months	2.1	2.3	0.433
Vaccination status			
Season 2017–18	43 (36.4)	207 (53.9)	0.001
Season 2016–17	41 (34.7)	197 (51.3)	0.002
Season 2015–16	43 (36.4)	191 (49.7)	0.008
Underlying conditions			
Diabetes	38 (32.2)	123 (32.0)	0.972
Heart disease	79 (66.9)	282 (73.4)	0.170
Lung disease	67 (56.8)	185 (48.2)	0.102
Immune suppressed	3 (2.5)	4 (1.0)	0.224
Cancer	21 (17.8)	69 (18.0)	0.966
Renal disease	26 (22.0)	71 (18.5)	0.394
Dementia or stroke	19 (16.1)	42 (10.9)	0.133
Rheumatologic disease	9 (7.6)	21 (5.5)	0.387
Obese	10 (8.5)	32 (8.3)	0.961
Any underlying condition	113 (95.8)	354 (92.2)	0.182
Diagnoses related to deterioration			
General deterioration	38 (32.2)	129 (33.6)	0.779
Dependency	41 (34.7)	108 (28.1)	0.101

Table 2. Comparison between test-positive for B virus 'Cases' (N = 91) and test-negative 'Controls' (N = 384) SARI recruited cases at hospital level. I-MOVE+ hospital study: Italy, 2017–18 season.

	Cases B (N = 91)	Controls (N = 384)	p-value
	N (%)	N (%)	
Mean age	77.1	77.8	0.396
Aged 65–79 years	61 (67.0)	234 (60.9)	0.281
Sex = male	49 (53.8)	229 (59.6)	0.314
Average number of hospitalisation in past 12 months	0.4	0.7	0.077
Average number of GP visits in past 12 months	2.0	2.3	0.296
Vaccination status			
Season 2017–18	34 (37.4)	207 (53.9)	0.005
Season 2016–17	31 (34.1)	197 (51.3)	0.003
Season 2015–16	32 (35.2)	191 (49.7)	0.009
Underlying conditions			
Diabetes	32 (35.2)	123 (32.0)	0.566
Heart disease	63 (69.2)	282 (73.4)	0.418
Lung disease	50 (54.9)	185 (48.2)	0.246
Immunocompromised	2 (2.2)	4 (1.0)	0.375
Cancer	16 (17.6)	69 (18.0)	0.931
Renal disease	21 (23.1)	71 (18.5)	0.319
Dementia or stroke	15 (16.5)	42 (10.9)	0.143
Rheumatologic disease	7 (7.7)	21 (5.5)	0.418
Obese	7 (7.7)	32 (8.3)	0.841
Any underlying condition	87 (95.6)	354 (92.2)	0.256
Diagnoses related to deterioration			
General deterioration	30 (33.0)	129 (33.6)	0.909
Dependency	35 (38.5)	108 (28.1)	0.027

When estimating VE data for TIVadj vaccine only, we observed a crude and adjusted VE of 51.3% (95%CI: 24.5 to 68.6) and 48.3% (95%CI: 18.7 to 67.2), respectively, for all influenza viruses. For A(H1N1)pdm09, the crude VE was 73.4% (95%CI: 26.4 to 90.4) and the adjusted VE was 67.5% (95%CI: 8.9 to 88.4). For B viruses a crude VE of 49.6% (95%CI: 18.3 to 68.9) and an adjusted VE of 44.5% (95%CI: 8.5 to 66.3) were observed (Figure 4).

4. Discussion

Our findings suggest that an adequate coverage for the influenza vaccination with a TIVadj vaccine in the elderly

population would prevent a half of the SARI hospitalizations associated with influenza.

We enrolled patients admitted to the participating hospital according to the I-MOVE+ SARI case definition, which is a slightly modified version of the WHO SARI case definition (including also deterioration of general conditions or deterioration of functional status). SARI patients are different from ILI cases, mainly because a SARI patients requires hospitalization [22]. Therefore, the reported influenza VE refers to severe, hospitalized cases of influenza in the elderly. These estimates can differ from the effectiveness of the flu vaccine in preventing ILI cases in the community.

Table 3. Comparison between test-positive for A/H1N1pdm09 'Cases' (N = 23) and test-negative 'Controls' (N = 384) SARI recruited cases at hospital level. I-MOVE+ hospital study: Italy, 2017–18 season.

	Cases A(H1N1) (N = 23)	Controls (N = 384)	p-value
	N (%)	N (%)	
Mean age	72.5	77.8	<0.001
Aged 65–79 years	20 (87.0)	234 (60.9)	0.012
Sex = male	16 (69.6)	229 (59.6)	0.345
Average number of hospitalisation in past 12 months	0.3	0.7	0.223
Average number of GP visits in past 12 months	1.9	2.3	0.534
Vaccination status			
Season 2017–18	6 (26.1)	207 (53.9)	0.009
Season 2016–17	7 (30.4)	197 (51.3)	0.040
Season 2015–16	8 (34.8)	191 (49.7)	0.118
Underlying conditions			
Diabetes	6 (26.1)	123 (32.0)	0.552
Heart disease	13 (56.5)	282 (73.4)	0.078
Lung disease	5 (65.2)	185 (48.2)	0.112
Immunocompromised	1 (4.3)	4 (1.0)	0.162
Cancer	4 (17.4)	69 (18.0)	0.944
Renal disease	3 (13.0)	71 (18.5)	0.511
Dementia or stroke	3 (13.0)	42 (10.9)	0.754
Rheumatologic disease	2 (8.7)	21 (5.5)	0.515
Obese	3 (13.0)	32 (8.3)	0.434
Any underlying condition	22 (95.6)	354 (92.2)	0.543
Diagnoses related to deterioration			
General deterioration	5 (21.7)	129 (33.6)	0.240
Dependency	5 (21.7)	108 (28.1)	0.559

Table 4. Seasonal influenza vaccine coverage by age group in the I-MOVE+ case control study, Italy, 2017–18.

Age-group	Vaccination status		Total
	No (%)	Yes (%)	
65–79	176 (55.7)	140 (44.3)	316
≥80	76 (40.9)	110 (59.1)	186
Total	252 (50.2)	250 (49.8)	502

Table 5. Distribution vaccine brand by cases and controls in the I-MOVE+ case control study, Italy, 2017–18.

Vaccine brand	Control	Case	Total
FLUAD	189	39	228
FLUARIX TETRA	1	0	1
INFLUVAC SUBUNIT	3	1	4
INTANZA	4	1	5
VAXIGRIP	2	1	3
VAXIGRIP TETRA	1	1	2
Total	200	43	243

The results of the test negative (TND) case-control study in Italy shows a moderate VE against influenza-associated SARI among hospitalized elderly patients. We estimated an adjusted VE of 48.5% for all vaccines. The estimated VE in our sample is higher compared to figures reported in EU in the same season, for a similar population, all vaccines (35%) [23]. As 94% of the vaccinees in our population had received the TIVadj vaccine, we had the possibility to calculate brand-specific VE, which resulted comparable to figures reported for all vaccines, also when considering strain-specific VE.

In Italy, compared to other influenza seasons, the 2017–18 season was characterised by a very high ILI overall incidence, with an early start (about 3 weeks before the start in the

previous season), a sharp increase and a large number of cases, especially in those aged ≥65 years [24]. The season was co-dominated by the B (60%) and the A viruses (40%).

The majority of subtyped A viruses belonged to the A/H1N1pdm09 strain (94%), mostly characterised by the genetic subgroup 6B.1 [24]. The same genetic subgroup characterises the vaccine variant A/Michigan/45/2015 included in the WHO recommendations for the influenza vaccine composition for the 2017/18 season [3]. Our hospital-based data on a population of elderly individuals show a good VE against A/H1N1pdm09 strains (65.1% for all vaccines and 67.5% for TIVadj).

These figures are in line with historical data reported in a recent meta-analysis, which showed a 61% VE against medically attended influenza A/H1N1pdm09, for all influenza vaccines available in EU, in all ages [25]. During the 2017/18 season, most of the northern hemisphere countries reported VE estimates in the general population in line with our data, with a moderate to good VE against influenza A(H1N1)pdm09 for all ages, all vaccines (68% in Europe [23], 67% in US [26]) and for all ages, hospitalized patients vaccinated with the non-adjuvanted trivalent vaccine (63% in Spain) [23,27]. Compared to our results, a lower VE against A (H1N1)pdm09 in hospitalised elderly patients was reported in Denmark (37%) [23].

The antigenic and molecular characterization of the circulating B viruses in Italy showed that 99% of the B viruses belonged to the Yamagata Lineage, while the trivalent vaccine included the Victoria Lineage. Despite this mismatch, we estimated a moderate VE against B viruses in elderly hospitalised patients (46.8% for all vaccines and 44.5% for TIVadj). Our estimates were higher compared to the VE estimates against B viruses reported in EU in the same population during the 2017/2018 season for all vaccines (34%) [23] and in Spain in hospitalized patients (all ages) vaccinated with the non-adjuvanted trivalent vaccine (37%). On the other hand, our results are more in line with the VE estimates against B influenza reported in the same season in US for all vaccines, all ages (42%) [26] and in Canada for all vaccines in 20–64 year-old adults (47%) [28].

The large majority of our population had received the trivalent adjuvanted vaccine. This might explain the moderate VE recorded despite the mismatch between the circulating B virus and the strains included in the vaccine, as it is well recognised that the trivalent adjuvanted vaccine is able to confer a cross-lineage protection.

The cross-protection against heterovariant strains has been repeatedly demonstrated for A(H3N2) [29], while evidence of heterologous immunogenicity has been deemed as limited for A(H1N1) and B, until the last years [30,31]. The hypothesis of the absence of a cross-lineage protection against circulating B strains supported the development of quadrivalent vaccines [31]. Nevertheless, in recent studies, trivalent adjuvanted vaccines showed an ability to elicit cross-lineage protection between the B strain included in the vaccine and the circulating strain [27,32]. A study conducted in Italy during the 2003/04 winter season showed a cross-linear protection against B/Yamagata strains, elicited by the MF59-TIV, containing a B/Victoria strain [31].

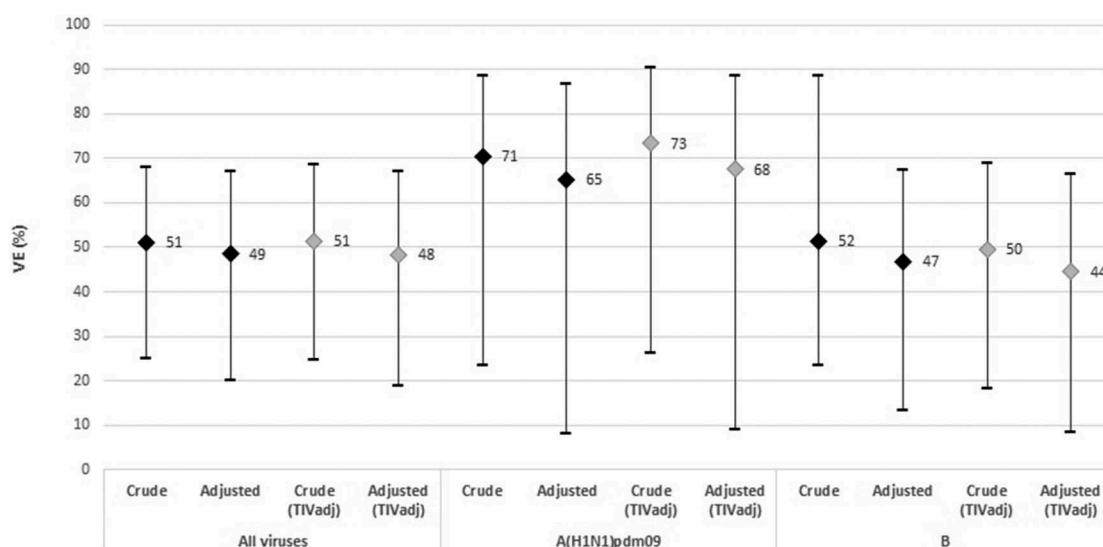


Figure 4. Crude and adjusted vaccine effectiveness in preventing influenza infection of TIVadj and all vaccines by virus subtype. I-MOVE+ hospital study: Italy, 2017–18 season.

Skoworonski et al. [33] showed a constant effectiveness ($\geq 50\%$) of TIVadj in Canada for eight consecutive seasons (2010/11 to 2017/18), independently from the level of lineage match. A recent meta-analysis [34] suggests that the main determinant of the cross-lineage protection is the probability of having been exposed to the B virus. The age of the vaccinated individual is a proxy of the previous exposure to the B influenza virus, therefore a quadrivalent vaccines can benefit young individuals, but may have no advantages in elderly individuals compared to the trivalent vaccine [34].

Our study has several limitations. Unfortunately, we were not able to collect and compute influenza B lineage-specific VE, however, the Influenza National Surveillance System showed a very clear predominance of the B/Yamagata lineage in the primary care and hospital samples [35].

Moreover, this is an observational study using data collected from hospitals and therefore residual confounding may still be present or accounted for, such as confounding by indication (patients with underlying chronic diseases are more likely to be vaccinated than healthy study participant) and healthy vaccinee bias (patients who are in better health conditions are more likely to adhere to the annual recommended influenza vaccination). However, we adjusted our data for comorbidities and therefore were able to adjust for confounding by indication. Unfortunately, we were not able to adjust for indicators of health-seeking behavior, however, the healthcare system in Italy is a regionally based national health service known as Servizio Sanitario Nazionale (SSN). It provides universal coverage, with public healthcare free of charge at the point of service, so it is supposed that anyone can have access, independently from his/her economic or social conditions. We have also measured the levels of unknown confounding required to impact on our study results and results were quite consistent. However, residual biases could be due to selection bias, particularly in ascertainment and laboratory confirmation. However, both are minimal in our study, because surveillance was active and cases with suspected symptoms had laboratory test done.

An important strength of our study is that the participating hospitals are large academic tertiary hospitals, of 600 to over 1000 beds, and all SARI patients from the related catchment area are admitted to these hospitals. The patients' screening for enrolment was systematic. Moreover, the patients' GPs, contacted by telephone, provided highly reliable data on vaccination dates and brands.

Moreover, we were able to reach a good sample size meeting the request in the protocol. This demonstrated that the recruitment procedures in place at the participating hospitals seem appropriate to exhaustively recruit SARI patients according to the case definition proposed. Finally, data consistency has been continuously monitored and evaluated as high for completeness and accuracy, through a warning and blocking procedures set on the dedicated web reporting platform and a weekly checking.

5. Conclusions

In conclusion, with the present study, focusing on a population of elderly individuals hospitalised with a SARI, we show a moderate to good adjusted VE of the trivalent adjuvanted vaccine against all viruses, a good adjusted VE against A/H1N1 strains and a moderate adjusted VE against B strains, despite a mismatch between the B circulating lineage and the lineage included in the vaccine. This is likely due to the cross-protection among B strains typically induced by the trivalent vaccine in elderly patients. We were also able to estimate adjusted VE for the TIVadj vaccine, that was slightly higher for A/H1N1pdm09 viruses and similar for B viruses. Our results support the use of the trivalent adjuvanted vaccine in elderly individuals, which, if an adequate coverage is obtained, has the potential of preventing half the hospitalization for SARI caused by influenza viruses. Finally, this kind of study, characterized by a systematic recruitment system, an accurate ascertainment of the participants' vaccination history and an effective monitoring of data consistency, should be an important complement to the traditional studies and could be useful to better assess the VE against influenza hospitalizations.

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Author contributions

A Bella wrote the article and performed the statistical analysis, F Gesualdo wrote the article and contributed to the interpretation of results, A Orsi, C Arcuri, M Chironna, C Napoli, I Manini coordinated the study at the local level and revised the draft article, V Alfonsi and M R Castrucci supported the coordination of the study at the national level and revised the draft article, C Rizzo conceived the study, coordinated the study and wrote the article.

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Declaration of interest

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