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Short communication

Lower frequency of SARS-CoV-2-associated severe respiratory infections among adults vaccinated against the 2021/22 season influenza

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An increasing number of observational studies has reported that seasonal influenza vaccination (SIV) may exert non-specific protective effects on COVID-19-related outcomes [1,2]. For instance, a recent systematic review and meta-analysis [1] has shown that the receipt of SIV was associated with a significant 17% risk reduction in SARS-CoV-2 infections.

Several immunologically plausible hypotheses that might explain the heterologous effects of SIV have been described and include the mechanisms of cross-reactivity, bystander activation and trained immunity [3]. The latter hypothesis has received a particular attention and postulates that the innate immunity cells are primed upon encountering exogenous/endogenous insults, causing long-term metabolic and epigenetic reprogramming and leading to an enhanced response to a second challenge [3]. The objective of this study was to compare the frequency of SARS-CoV-2 among SIV vaccinated and non-vaccinated adults hospitalized for severe acute respiratory infection (SARI).

Data used in this study were collected between November 22, 2021 and April 28, 2022 within the DRIVE study whose primary aim is to estimate SIV effectiveness against laboratory-confirmed influenza. The core protocol is available elsewhere [4]. Briefly, a test negative case-control study was conducted at Le Scotte University Hospital of Siena (Tuscany, Central Italy). Adult (≥18 years) subjects hospitalized for SARI were prospectively enrolled. SARI was defined as a respiratory infection with ≥1 systemic (e.g., fever, malaise, headache, myalgia) and ≥1 respiratory (cough, sore throat, shortness of breath) symptom requiring hospitalization. Each subject underwent an oropharyngeal swab and tested for both influenza and SARS-CoV-2 by means of real-time reverse-transcription quantitative polymerase chain reaction (RT-qPCR). Both SIV and COVID-19 vaccination status were ascertained through available medical records. To address sparse data, the Firth's penalized logistic regression was applied to estimate the odds ratio (OR) of being positive for SARS-CoV-2 according to the 2021/22 SIV status, when adjusted (aOR) for age, sex, presence of chronic conditions, month of swabbing, previous SARS-CoV-2 positivity, previous season SIV receipt and COVID-19 vaccination schedule [5]. In the sensitivity analysis, the magnitude of unmeasured confounding was quantified by means of E-values with upper bounds (UBs) of 95% CIs [6].

The study was approved by the Ethics Committee of Area Vasta Sud Est of Tuscany (Approval letter of November 15, 2021; Protocol n

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Table 1
Demographic and clinical characteristics of the study participants (n = 129).

Variable	Level	Cases (N = 55)	Controls (N = 74)	p-value
Sex,% (n)	Female	54.5 (30)	51.4 (38)	0.73 [a]
	Male	45.5 (25)	48.6 (36)	
Age, years	Median (IQR)	76 (50–88)	78 (61–86)	0.65 [b]
	18–64,% (n)	43.6 (24)	31.1 (23)	0.20 [a]
	≥65,% (n)	56.4 (31)	68.9 (51)	
2021/22 seasonal influenza vaccination,% (n)	No	69.1 (38)	52.7 (39)	0.071 [a]
	Yes	30.9 (17)	47.3 (35)	
2020/21 seasonal influenza vaccination,% (n)	No	54.5 (30)	45.9 (34)	0.23 [a]
	Yes	5.5 (3)	14.9 (11)	
	Unknown	40.0 (22)	39.2 (29)	
COVID-19 vaccination,% (n)	No	20.0 (11)	17.6 (13)	0.17 [a]
	1 dose	0 (0)	8.1 (6)	
	2 doses	25.5 (14)	20.3 (15)	
	3 doses	54.5 (30)	54.1 (40)	
Previous SARS-CoV-2 positivity,% (n)	No	78.2 (43)	79.7 (59)	0.69 [a]
	Yes	10.9 (6)	6.8 (5)	
	Unknown	10.9 (6)	13.5 (10)	
Month of swabbing,% (n)	Nov 2021	0 (0)	23.0 (17)	<0.001 [a]
	Dec 2021	0 (0)	13.5 (10)	
	Jan 2022	49.1 (27)	27.0 (20)	
	Feb 2022	16.4 (9)	1.4 (1)	
	Mar 2022	29.1 (16)	24.3 (18)	
	Apr 2022	5.5 (3)	10.8 (8)	
≥1 chronic condition,% (n)	No	1.8 (1)	1.4 (1)	0.99 [a]
	Yes	98.2 (54)	98.6 (73)	

[a] Fisher's exact test.
[b] Mann-Whitney's test. IQR; Interquartile range.

° 21,090). Informed consent was obtained from all subjects involved in the study.

A total of 129 subjects were enrolled. Briefly, both sexes were equally represented (52.7% females), and their median age was 77 (range 18–101) years. Most subjects had ≥1 co-morbidity (98.4%); cardiovascular pathologies (84.5%), diabetes (66.1%) and respiratory conditions (57.3%) were the most frequent. About one half (54.3%) of subjects received a COVID-19 vaccine booster (third) dose, which was mainly (85.7%) administered in September–December 2021. The 2021/22 SIV coverage was 40.3% (Table 1).

The SARS-CoV-2 positivity was recorded for 29.9% of (n = 55) subjects (cases), most of which occurred in January 2022. Only 9 influenza detections (all belonged to A/H3N2) occurred; among these 9 subjects only one received SIV. Owing to the paucity of influenza detections, no SIV effectiveness against A/H3N2 could be established. As shown in Table 1, SARS-CoV-2 positive cases were comparable to negative controls for all except one variable. Indeed, compared with cases, more infections occurred in October–November 2021 among controls. SARS-CoV-2 positivity among subjects who received the 2021/22 SIV (32.7%; 17/52) was 1.5 times lower than in non-vaccinated individuals (49.4%; 38/77). Subjects who received SIV were on median older (86 vs 61 years; Mann-Whitney's test: p<0.001) and were more frequently administered the previous season SIV (23.1% vs 2.6%; Fisher's exact test: p_{adj}=0.001) and booster COVID-19 vaccine dose (80.8% vs 36.4%; Fisher's exact test: p_{adj}<0.001) than those who did not receive SIV.

The protective effect of the 2021/22 SIV was confirmed in the adjusted analysis (Fig. 1). In particular, in the fully adjusted model SIV reduced the likelihood of testing positive for SARS-CoV-2 with an aOR of 0.25 (95% CI: 0.07–0.78). The corresponding E-value was 3.41 (95% CI_{UB}: 1.52), suggesting that unmeasured confounding was unlikely to explain the association.

Most available studies on the association between SIV and COVID-19-related endpoints were conducted during the 2019/20 winter

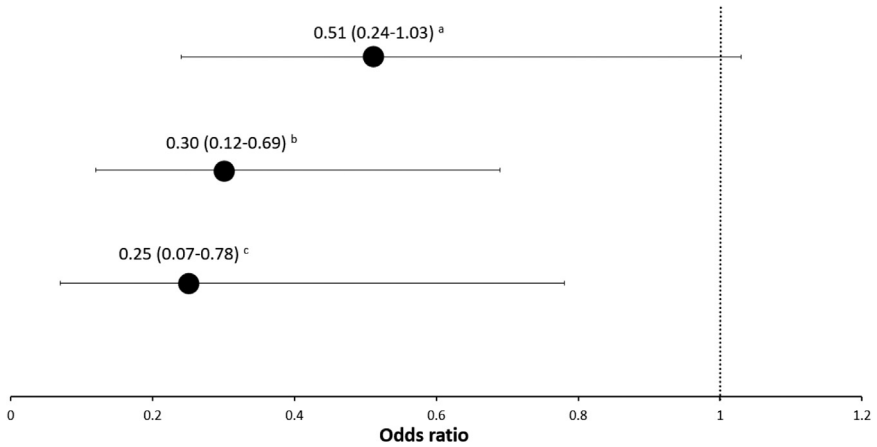

Fig. 1. Association between the 2021/22 seasonal influenza vaccination and SARS-CoV-2 positivity. [a] Crude; [b] Adjusted for the month of oropharyngeal swab, as per best-combination model selection approach based on minimization of the corrected Akaike's information criterion (AICc); [c] Fully adjusted model (adjusted for age, sex, presence of chronic conditions, month of swabbing, previous SARS-CoV-2 positivity, previous season SIV receipt and COVID-19 vaccination schedule).

season or otherwise before the implementation of COVID-19 vaccination [1]. In the present study we demonstrated that uptake of the 2021/22 SIV was associated with a reduced positivity to SARS-CoV-2 independently from the COVID-19 vaccination status.

Our results are generally in line with pooled estimates obtained by two recent systematic reviews [1,2]. From the point of view of the observed effect size, our estimate (aOR 0.32) approaches that seen in the neighbor Region of Lazio (Central Italy) [7]. In particular, SIV receipt was associated with a reduced likelihood of the 60-day COVID-19 mortality among subjects admitted to emergency departments [aOR 0.20 (95% CI: 0.08–0.51)].

Our results are preliminary and owing to a small sample size should be interpreted cautiously and further confirmed in larger case-control or cohort studies. Another important limitation is the possibility of both selection bias and residual confounding. However, our sensitivity analysis suggested the probability of bias arising from these systemic errors was low.

To conclude, in our study the 2021/22 SIV was associated with a reduced SARS-CoV-2 positivity among adult SARI patients. The trained immunity hypothesis seems to be the most plausible mechanism of this association. Increase in the 2022/23 SIV coverage in at-risk populations should be pursued.

Declaration of Competing Interest

Alexander Domnich was previously a permanent employee of Seqirus S.r.L., a pharmaceutical company who manufacture and commercialize influenza vaccines. The other authors declare no conflict of interest.

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