Impact of the additional/booster dose of COVID-19 vaccine against severe disease during the epidemic phase characterized by the predominance of the Omicron variant in Italy, November 2021 - March 2022

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Abstract

Despite the stunning speed with which highly effective and safe vaccines have been developed, increasingly transmissible variants are emerging. Using surveillance data from Italy (November 2021-March 2022), during the epidemic phase characterized by the predominance of the Omicron variant, vaccination with additional/booster dose significantly reduces the risk at all ages for hospitalization (relative risk (RR): 0.16; 95% confidence interval (CI): 0.13-0.19), admission to ICU (RR: 0.08; 95% CI: 0.06-0.09) and death (RR: 0.13; 95% CI: 0.10-0.16). Results support the importance of receiving a third dose of mRNA COVID-19 vaccine.

Keywords: SARS-CoV-2; COVID-19; Italy; Omicron variant; Vaccine effectiveness

Introduction

The development of effective and safe vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been extraordinarily rapid, with less than a year elapsing between the sequencing of the new viral genome and the initiation of major vaccination campaigns in different parts of the world. However, several notable variants of SARS□CoV□2 (also known as *variants of concern* (VOCs)) continue to emerge, such as the Omicron variant, causing high rates of infection/re, a major impact on health care services, and a slowdown to the socio-economic system [1].

Several studies contributed to show the effectiveness of vaccination against symptomatic disease caused by the VOCs [2,3]. Other studies investigated the potential decline in vaccine-induced protective immunity [4,5,6], showing that protection against symptomatic disease wanes over time against symptomatic disease [7,8].

Regardless of the vaccine received as a 2nd dose, the mRNA vaccines provide a strong booster effect with low reactogenicity [9], so the competent authorities recommended either a BNT162b2 (Comirnaty) or a half dose (50 µg) of mRNA-1273 (Spikevax) vaccine to be given as a booster dose. In Italy, COVID-19 booster vaccines were introduced on 13 September 2021. The doses were initially offered only to those with suppressed immune systems, including AIDs patients and those on dialysis for renal failure, as well as cancer patients and transplant recipients. However, to contain rising cases, the eligibility criteria were quickly expanded to include care home workers, the over 80s, and health professionals by the end of September; over-60s by mid-October; over-40s by late November; and over-18s by the end of December. From February 1, 2022, the minimum period to receive the booster dose of vaccine is reduced from 5 to 4 months after the last dose.

The aim of this work is to evaluate the impact of COVID-19 additional/booster vaccines against COVID-19-related symptoms, hospitalization, and death in Italy, between November 14, 2021, and March 23, 2022, when Omicron was the dominant variant in circulation.

Method for estimating the vaccine effectiveness

Estimates of Vaccine Effectiveness (VE) were obtained through the weekly bulletin[1] published by the National Public Health Institute (Istituto Superiore di Sanità, ISS). Such estimates are calculated using generalized linear random-effects model with Poisson distribution, considering the number of events per day as the dependent variable, vaccination status as the independent variable, 10-year age groups and weekly regional incidence as adjustment variables, and including region of administration as a random effect.

Using this model, it is possible to estimate the relative risk (RR), i.e., the ratio of the incidence of the event among the vaccinated with 2 doses (<90 days, 91-120 days and >120 days and additional/booster dose) to the incidence of the same event among the unvaccinated. Moreover, the vaccine effectiveness was also measured by analyzing the number needed to treat (NNT), i.e., the number of people who need to be vaccinated to prevent one additional adverse outcome from the disease. VE estimates are calculated using the formula: (1 - RR) × 100, where the closer the value is to 100 the greater the effectiveness of the vaccine (see Supplementary material for details).

Methodological notes on data collection by the ISS

The ISS retrieves data from the Italian integrated COVID-19 surveillance system[2], which merges information on the COVID-19 vaccinated persons listed in the National Vaccination Registry [10] and data on individual cases of confirmed COVID-19 defined as any person with a laboratory-confirmed human SARS-CoV-2 infection, whether symptomatic or asymptomatic [11]. Following diagnosis, cases are followed and any COVID-related hospitalization, admission to intensive care unit (ICU), or death among these is reported to the surveillance system.

Figure 1 shows the timing with which the study populations were selected. Once the period for which the rate of diagnosis of COVID-19 in vaccinated individuals to be calculated is chosen, it is followed by a follow-up period of at least 14 days from the date of vaccine administration to allow for adequate diagnostic evaluation (including the incubation period). Record linkage is performed within 17 days to allow time for diagnosed cases to be reported to the surveillance system. Regarding the rates of diagnosis with subsequent hospitalization, admission to ICU and death a longer follow-up period is necessary to allow an adequate time to observe possible worsening of clinical conditions up to hospitalization/death. Only hospitalizations, admissions to ICU, and deaths occurring within 28 days from diagnosis are considerate.

[1] https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_5-gennaio-2022.pdf
[2] https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-integrated-surveillance-data

Results of the epidemiological investigation

As of 22/03/2022, 135,545,394 doses have been administered (47,275,808 first doses, 49,695,812 second/single doses and 38,573,774 third doses) [12]. Considering the population and the period under analysis (see Table 1), 6,424,935 cases were reported among the unvaccinated, 4,457,813 cases among those vaccinated with 2 doses within 120 days, 9,608,739 cases among those vaccinated with 2 doses for more than 120 days and 6,545,303 cases among those vaccinated with an additional/booster dose.

Since it is not possible to compare the absolute numbers of events in the different vaccination status within the same age group because they refer to different populations, it was necessary to calculate the specific rate, i.e., the number of events in each age group divided by the population of each age group in the reference period per 100,000 inhabitants. Figure 2 describes the incidence rate of SARS-CoV-2 infection and the rates of hospitalization, admission to ICU and mortality per 100,000 calculated for the unvaccinated, those vaccinated more than 120 days, within 120 days and with an additional/booster dose. Supplement Figures S1-S2-S3-S4, on the other hand, report the relative risk by vaccination status and by age group. The results of vaccine effectiveness are summarized in Table 2.

Considering the rate of hospitalization for the unvaccinated in older adults, i.e., 60-79 (404 hospitalizations per 100,000) and 80+ (982 hospitalizations per 100,000) age groups, it was about 7 and 6, respectively, times higher than for those vaccinated with 2 doses less than 120 days ago (82 hospitalizations per 100,000 in the 60-79 age group; 261 hospitalizations per 100,000 in the 80+ age group) and about 17 and 35, respectively, times higher than for those vaccinated with an additional/booster dose (57 hospitalizations per 100,000 in the 60-79 age group; 98 hospitalizations per 100,000 in the 80+ age group).

In the same period, the rate of admissions to ICU among the unvaccinated in the 60-79 (52 admissions to ICU per 100,000) and 80+ (38 admissions to ICU per 100,000) age group was about 13 and 7, respectively, times higher than for those vaccinated with 2 doses within 120 days (6 admissions to ICU per 100,000 in the 60-79 age group; 9 admissions to ICU per 100,000 in the 80+ age group) and about 37 and 53, respectively, times higher than for those vaccinated with an additional/booster dose (3 admissions to ICU per 100,000 in the 60-79 age group; 2 admissions to ICU per 100,000 in the 80+ age group).

The mortality rate in the unvaccinated in the 60-79 (117 deaths per 100,000) and 80+ (428 deaths per 100,000) age groups was about 10 and 7, respectively, times higher than in those vaccinated with a vaccinated with 2 doses within 120 days (18 deaths per 100,000 in the 60-79 age group; 94 deaths per 100,000 in the 80+ age group) and 25 and 64, respectively, times higher than for those vaccinated with an additional/booster dose (14 deaths per 100,000 in the 60-79 age group; 28 deaths per 100,000 in the 80+ age group).

Discussion

This work suggests that in Italy the vaccination with additional/booster dose considerably reduced the risk of a COVID-19 diagnosis and subsequent hospitalization and death. As shown in Figure 3(A), the overall vaccine effectiveness (VE) of vaccinated with 2 doses within 90 days in preventing infection was 50.4% (95% CI: 50.2%-50.6%), i.e., there was a risk reduction of about 50% for those vaccinated within 90 days compared to the unvaccinated. Between 90 and 120 days after the administration of the second dose, the estimated VE in preventing diagnoses was 41.8% (95% IC: 41.6%-42.0%), rising to 47.5% (95% IC: 47.4%-50.6%) after 120 days, and 70.0% (95% IC: 69.9%-70.1%) in individuals with additional/booster dose.

In the case of severe disease (see Figure 3(B)), vaccine effectiveness for those vaccinated with 2 doses within 90 days, between 91 and 120 days and over 120 days was 73.2% (95% IC: 72.1%-74.2%), 75.5% (95% IC: 74.3%-76.5%) and 75.6% (95% IC: 75.1%-76.1%) respectively, whereas it was 91.3% (95% IC: 91.1%-91.5%) in vaccinated with an additional/booster dose.

To prevent one diagnosis of COVID-19 (see Figure 3(C)), the NNT among the unvaccinated and vaccinated (<120 days, >120 days and additional/booster dose) was 85, 44 and 40, respectively. Regarding the severe disease (see Figure 3(D)), the NNT was 7,310 (<120 days) and 7,589 (>120 days), whereas 7,076 (with additional/booster dose).

The results of this work have at least three limitations. First, comparisons of VE estimates between age groups must be interpreted with caution because of differences in the timing of vaccine availability and predominant variants when the vaccine became available for different age groups. Second, VE was not assessed by vaccine product (e.g., Comirnaty, Spikevax) due to lack of data. Third, it was not possible to distinguish whether a third dose was received as an additional dose to complete the primary vaccine cycle for immunocompromised persons or as a booster dose after completion of the primary vaccine cycle to assess VE in the two categories.

Conclusion

The results underscore the importance of receiving a third dose of COVID-19 mRNA vaccine to prevent both infection and severe COVID-19, especially when the Omicron variant is the predominant circulating variant and when the effectiveness of 2 doses of mRNA vaccines is significantly reduced against this variant. It is recommended that adults over 60 years of age who have received the second dose of COVID-19 vaccine should receive a third dose when eligible. Moreover, all unvaccinated persons should get vaccinated as soon as possible.

Ethical statement

None declared.

Acknowledgements

None declared.

Conflict of interest

None declared.

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Tabe 1. Characteristics of the study population, between November 14, 2021, and March 23, 2022.

UV[a]	Diagnoses	FV-120[b]	Diagnoses	FV+120[c]	Diagnoses	FV+B[d]	Diagnoses
Total (N=126,724,941)	6,424,935	Total (N=98,224,159)	4,457,813	Total (N=215,413,391)	9,608,739	Total (N=307,080,485)	6,545,303
12-39 (N=52,232,228)	2,914,241	12-39 (N=57,673,980)	3,081,195	12-39 (N=75,738,422)	4,507,359	12-39 (N=54,936,576)	1,808,610
40-59 (N=49,237,187)	2,539,676	40-59 (N=29,922,326)	1,153,841	40-59 (N=77,769,047)	3,543,049	40-59 (N=98,128,083)	2,619,498
60-79 (N=21,271,605)	809,126	60-79 (N=9,331,733)	195,000	60-79 (N=50,448,166)	1,361,117	60-79 (N=104,115,854)	1,489,898
80+ (N=3,983,921)	161,892	80+ (N=1,296,120)	27,777	80+ (N=11,457,756)	197,214	80+ (N=49,899,972)	627,297

UV[a]	Hospitalizations	FV-120[b]	Hospitalizations	FV+120[c]	Hospitalizations	FV+B[d]	Hospitalizations
Total (N=130,612,065)	170,414	Total (N=116,881,149)	27,321	Total (N=252,628,244)	117,763	Total (N=248,197,489)	92,577
12-39 (N=54,158,054)	21,985	12-39 (N=70,019,970)	11,024	12-39 (N=78,842,934)	12,011	12-39 (N=38,512,929)	5,329
40-59 (N=50,365,037)	43,131	40-59 (N=34,736,163)	6,302	40-59 (N=93,589,340)	17,645	40-59 (N=76,233,897)	11,215
60-79 (N=21,946,616)	64,608	60-79 (N=10,776,207)	6,473	60-79 (N=65,849,833)	49,855	60-79 (N=86,624,187)	30,083

UV[a]	ICUs	FV-120[b]	ICUs	FV+120[c]	ICUs	FV+B[d]	ICUs
Total (N=130,612,065)	19,888	Total (N=116,881,149)	1,329	Total (N=252,628,244)	6,891	Total (N=248,197,489)	4,165
12-39 (N=54,158,054)	811	12-39 (N=70,019,970)	167	12-39 (N=78,842,934)	249	12-39 (N=38,512,929)	109
40-59 (N=50,365,037)	5,610	40-59 (N=34,736,163)	406	40-59 (N=93,589,340)	958	40-59 (N=76,233,897)	624
60-79 (N=21,946,616)	11,880	60-79 (N=10,776,207)	628	60-79 (N=65,849,833)	4,706	60-79 (N=86,624,187)	2,300
80+ (N=4,142,358)	1,587	80+ (N=1,348,809)	128	80+ (N=14,346,137)	978	80+ (N=46,826,476)	1,132

UV[a]	Deaths	FV-120[b]	Deaths	FV+120[c]	Deaths	FV+B[d]	Deaths
Total (N=132,701,998)	33,512	Total (N=127,397,108)	2,674	Total (N=269,415,416)	24,429	Total (N=217,612,742)	17,166
12-39 (N=55,214,700)	261	12-39 (N=75,584,906)	25	12-39 (N=78,553,881)	138	12-39 (N=30,884,822)	45
40-59 (N=50,972,414)	2,294	40-59 (N=38,132,218)	238	40-59 (N=100,868,048)	839	40-59 (N=64,958,278)	392
60-79 (N=22,294,766)	12,873	60-79 (N=12,280,908)	1,092	60-79 (N=73,786,706)	8,351	60-79 (N=76,908,150)	3,981
80+ (N=4,220,118)	18,084	80+ (N=1,399,076)	1,319	80+ (N=16,206,781)	15,101	80+ (N=44,861,492)	12,748

[a]**Unvaccinated cases** (**UV**): all notified cases with a confirmed diagnosis of infection with SARS-CoV-2 virus who did not receive any dose of vaccine or were vaccinated with the first dose or a single dose of vaccine within 14 days before diagnosis.

[b] **Cases of individuals fully vaccinated ≤ 120** (**FV-120**): all notified cases with a confirmed diagnosis of infection with SARS-CoV-2 virus beginning on day 14 after administration of the second dose and for the next 120 days.

[c] **Cases of individuals fully vaccinated > 120** (**FV+120**): all notified cases with a confirmed diagnosis of infection with SARS-CoV-2 virus made more than 120 days after the 14th day after administration of the second dose who have not received the additional/booster dose within the previous 14 days.

[d] **Cases of individuals fully vaccinated with additional dose** (**FV+B)**: all notified cases with a confirmed diagnosis of infection with SARS-CoV-2 virus at least 14 days after administration of the additional dose or booster.

Table 2. Vaccine effectiveness from November 14, 2021, by vaccination status and by age group.

		Rate (x 100,000)				RR						NNT		
	Age group	UV	FV-120	FV+120	FV+B	UV/ FV-120	95% CI	UV/ FV+120	95% CI	UV/ FV+B	95% CI	UV/ FV-120	UV/ FV+120	UV/ FV+B
Diagnoses														
	12-39	5,070.0	4,538.4	4,460.6	2,131.5	1.8	1.5 – 2.1	1.8	1.5 – 2.1	3.5	2.6 – 4.4	7	35	51
	40-59	4,712.8	3,394.9	3,652.3	1,878.6	2.1	1.7 – 2.5	1.9	1.7 – 2.1	4.0	3.2 – 4.8	101	52	65
	60-79	3,844.8	2,096.2	2,517.3	1,374.7	2.6	2.4 – 2.8	2.1	1.9 – 2.3	5.1	4.3 – 5.8	53	51	45
	80+	4,063.6	2,143.1	1,721.2	1,257.1	3.2	2.5 – 3.9	3.3	3.1 – 3.5	7.1	5.3 – 8.9	41	32	35
Diagnoses with subsequent hospitalization														
	12-39	130.5	23.4	46.6	37.3	4.5	2.7 – 6.2	4.8	3.6 – 6.0	7.3	4.7 – 10.3	5,097	3,657	3,472
	40-59	194.1	34.8	60.9	41.6	8.5	4.1 – 12.9	6.9	3.9 – 9.9	13.1	8.5 – 17.7	5,229	4,704	3,461
	60-79	403.6	82.4	109.9	57.0	6.9	4.9 – 8.9	5.0	3.7 – 6.3	16.8	11.1 – 22.5	697	985	557
	80+	982.3	261.1	266.6	98.1	5.9	4.8 – 7.0	4.6	4.2 – 5.0	34.8	24.1 – 45.5	117	119	100
Diagnoses with subsequent admission to ICU														
	12-39	15.2	1.1	2.7	1.6	9.6	5.8 – 13.4	8.7	5.4 –12.0	5.4	4.1 – 6.7	165,556	223,451	154,258
	40-59	25.0	2.5	3.8	1.9	17.3	8.3 – 26.3	15.6	8.8 – 22.4	20.7	12.3 – 29.1	65,209	44,118	38,442
	60-79	51.6	6.2	7.1	2.6	12.8	8.5 – 17.1	9.5	6.8 – 12.2	37.1	28.2 – 46.0	4,363	4,583	3,554
	80+	38.3	9.5	6.8	2.4	6.8	4.3 – 9.3	6.9	6.0 – 7.7	52.9	30.9 – 74.8	4,136	3,661	3,457
Diagnoses with subsequent death														
	12-39	25.3	2.1	9.1	7.9	16.3	10.2 – 22.4	5.9	3.2 – 8.6	5.1	3.5 – 6.7	240,017	312,047	307,377
	40-59	42.9	5.1	12.7	9.2	14.5	8.5 – 20.5	7.9	5.7 – 10.1	11.2	8.6 – 13.7	68,475	58,048	39,462
	60-79	116.8	17.6	26.1	13.7	10.1	6.5 – 13.7	7.0	5.1 – 8.9	24.9	18.1 – 31.7	2,269	3,134	1,874
	80+	428.5	94.3	93.2	28.4	6.8	5.8 – 7.8	5.8	4.9 – 6.7	63.6	40.1 – 87.1	218	224	183

RR: Relative Risk; CI: Confidence Interval; NNT: Number Needed to Treat.

Figure 1. Timeline of selection of the study populations for the ascertainment of each study event.

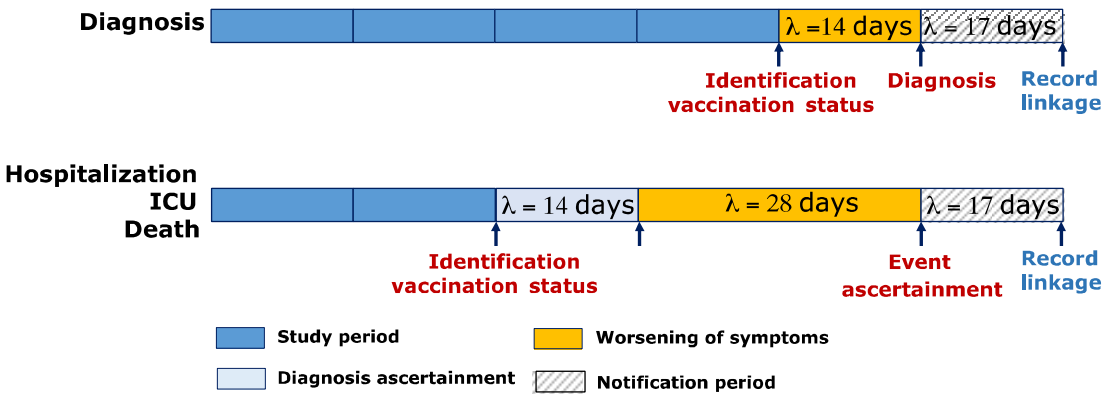

Figure 2. Incidence of reported COVID-19 cases (A), hospitalization rate (B), ICU admission rate (C), and mortality rate (D) per 100,000 by vaccination status and by age group.

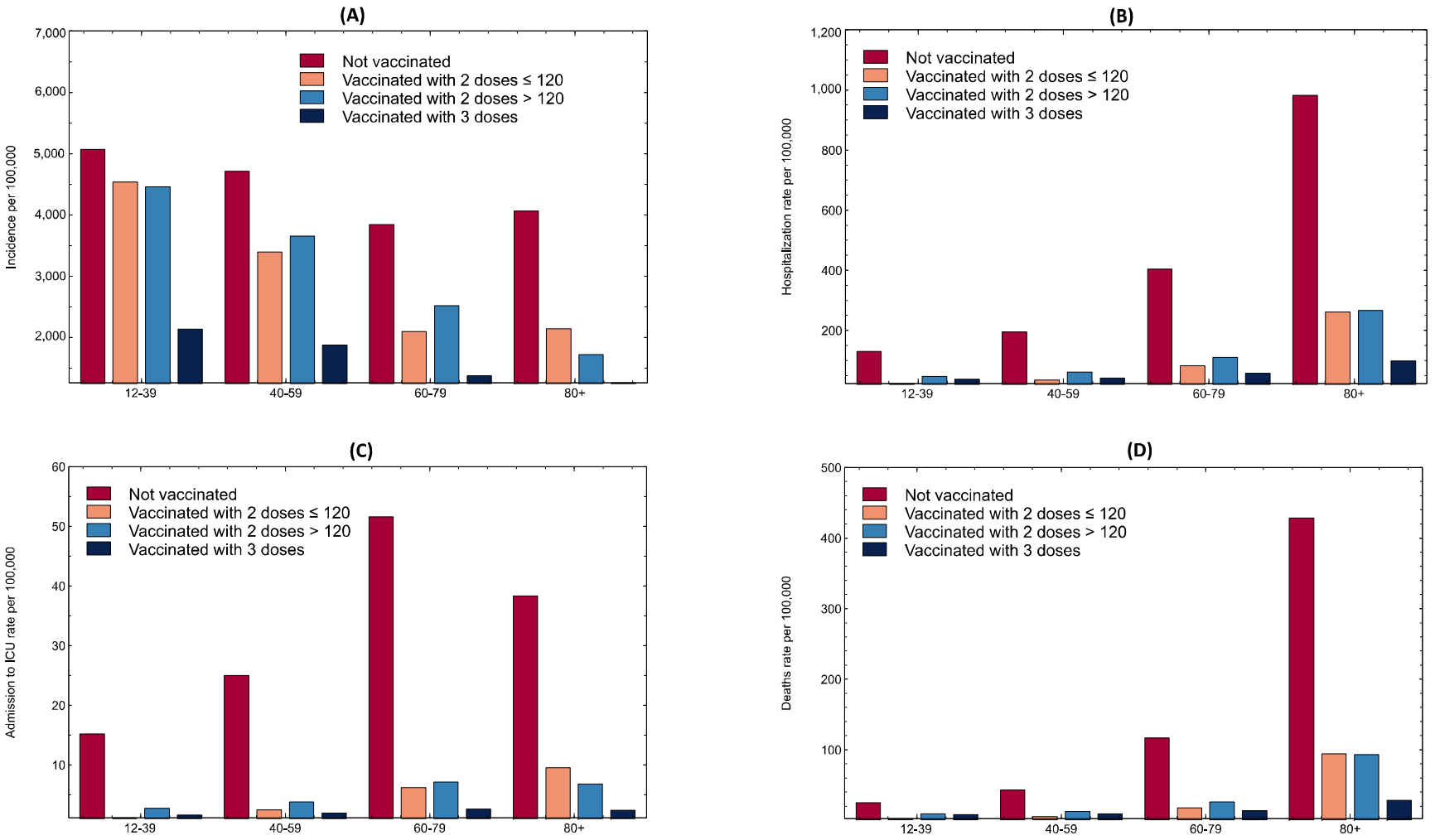

Figure 3. Vaccine effectiveness (VE) and Number Needed to Treat (NNT) to prevent (A) any COVID-19 diagnoses and (B) severe acute by vaccination status.