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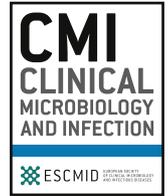
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Original article

Impact of vaccination on the presence and severity of symptoms in hospitalized patients with an infection of the Omicron variant (B.1.1.529) of the SARS-CoV-2 (subvariant BA.1)

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ABSTRACT

Objectives: The emergence of SARS-CoV-2 variants raised questions about the extent to which vaccines designed in 2020 have remained effective. We aimed to assess whether vaccine status was associated with the severity of Omicron SARS-CoV-2 infection in hospitalized patients.

Methods: We conducted an international, multi-centric, retrospective study in 14 centres (Bulgaria, Croatia, France, and Turkey). We collected data on patients hospitalized for ≥ 24 hours between 1 December 2021 and 3 March 2022 with PCR-confirmed infection at a time of exclusive Omicron circulation and hospitalization related or not related to the infection. Patients who had received prophylaxis by monoclonal antibodies were excluded. Patients were considered fully vaccinated if they had received at least two injections of either mRNA and/or ChAdOx1-S or one injection of Ad26.CoV2-S vaccines.

Results: Among 1215 patients (median age, 73.0 years; interquartile range, 57.0–84.0; 51.3% men), 746 (61.4%) were fully vaccinated. In multivariate analysis, being vaccinated was associated with lower 28-day mortality (Odds Ratio [95% Confidence Interval] (OR [95CI]) = 0.50 [0.32–0.77]), intensive care unit admission (OR [95CI] = 0.40 [0.26–0.62]), and oxygen requirement (OR [95CI] = 0.34 [0.25–0.46]),

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independent of age and comorbidities. When co-analysing these patients with Omicron infection with 948 patients with Delta infection from a study we recently conducted, Omicron infection was associated with lower 28-day mortality (OR [95CI] = 0.53 [0.37–0.76]), intensive care unit admission (OR [95CI] = 0.19 [0.12–0.28]), and oxygen requirements (OR [95CI] = 0.50 [0.38–0.67]), independent of age, comorbidities, and vaccination status.

Discussion: Originally designed vaccines have remained effective on the severity of Omicron SARS-CoV-2 infection. Omicron is associated with a lower risk of severe forms, independent of vaccination and patient characteristics. **Guillaume Beraud, Clin Microbiol Infect 2023;29:642**

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Introduction

First identified in November 2021, the Omicron (B.1.1.529) variant of concern (VOC) of SARS-CoV-2 replaced the Delta (B.1.617.2) VOC globally and became virtually the only circulating variant in most countries in December 2021 and January 2022. Between December 2021 and April 2022, it was responsible for periods of highest incidence of SARS-CoV-2 infection in Europe, North America, China, and Japan since the beginning of the pandemic [1]. The extent of Omicron VOC waves is considered to be related to increased infectivity and immune escape from neutralizing antibodies resulting from previous SARS-CoV-2 infection, vaccination, or both [2,3].

In most European countries, the unprecedented numbers of SARS-CoV-2 infections during Omicron waves were associated with a decreased case-fatality rate compared with the Delta VOC [4–6]. Whether related to an intrinsically lower risk of severe COVID-19 or the high vaccine coverage, this Omicron VOC calls into question the impact of vaccination at both the individual and the populational level. Meanwhile, the picture provided by the aforementioned studies is incomplete because most milder cases will not be admitted to the hospital or even diagnosed.

We aimed to determine the extent to which vaccination was still associated with protection against severe forms of Omicron infection by assessing severity among people hospitalized with SARS-CoV-2 infection when considering their vaccine status and other risk factors. We also explored the influence of VOC by coupling our data with previously published data on the Delta variant and using the same methodology.

Methods

We performed a retrospective, multicentre study across 14 hospital centres from four countries, namely Bulgaria (Sofia), Croatia (Olsijek and Zagreb), France (Annecy, Paris/Béclère, Caen, Grenoble, Le Mans, Limoges, Nantes and Poitiers) and Turkey (Ankara and Karaman). Hospitalized patients with a PCR-confirmed SARS-CoV-2 infection from 1 December 2021 to 3 March 2022 (i.e. when the Omicron [B.1.1.529] variant [subvariant BA.1] was virtually the only circulating SARS-CoV-2 variant in these countries) were included chronologically regardless of the indication for admission, the objective being to include at least the first 50–100 patients per centre. Patients were considered infected by the Omicron VOC either through mutation screening or because it was the only variant circulating at that time in the area according to the virologist from each centre.

A patient was considered fully vaccinated if he/she had received at least either one injection of the Ad26.CoV2-S vaccine (Janssen) or two injections of the ChAdOx1-S vaccine (AstraZeneca) and/or RNA vaccines (tozinameran [Pfizer/BioNTech] and elasomeran [Moderna]), with the last injection administered at least 14 days before

the date of PCR. Vaccinated and unvaccinated patients were included concurrently according to the order of hospitalization in the participating centre.

Data were anonymously collected with a form similar to the one used in a recent study on SARS-CoV-2 Delta infection [7], providing similar variables (supplementary material and Tables 1 and 2), with the exception of antiviral treatments, which were not available at the time data were collected for the Delta study. The ethics committee of the French-speaking Society of Infectious Diseases (IRB00011642) gave its approval for the study (N°2022-0101), which was declared to the French National Commission for Informatics and Liberties (CNIL MR004: n°2224742).

Statistical analysis

Qualitative variables are expressed as counts (percentage) and frequency distributions compared with the chi-square test or Fisher's exact test when appropriate. Continuous variables were expressed as median (first quartile; third quartile), and differences were tested with the independent t-test for normally distributed variables or otherwise with the Mann-Whitney U test. Factors associated with severe forms of infection defined by three outcomes (requirement for oxygen, intensive care unit [ICU] admission, and death at day 28) were assessed. Univariate and multivariate logistic regressions based on general linear models were performed with a stepwise variable selection according to the Akaike information criterion [8] to select the potential risk factors for severe outcome (Table 3) for the multivariate model (Table 4 and supplementary material). Even though some data were missing at random, in many cases, this was because they did not exist. Patients could have been too severe to receive a computed tomography (CT) scan before mechanical ventilation or only mildly ill and went back home without any oxygen requirement or CT scan. To manage missing data not at random, multivariate analysis was initially performed only on the dataset with complete cases, after which the model was applied to the full dataset [9]. Results are presented on the basis of the full dataset. In addition, a multivariate analysis was similarly performed on the dataset of vaccinated patients only to independently assess the weight of comorbidities among vaccinated patients, taking into account the influence of the time elapsed since the most recent injection. Interactions were systematically searched and mentioned if found. Finally, this cohort of Omicron-infected patients was merged with a cohort of Delta-infected patients recently published [7], and an analysis was performed taking into account the VOC. All statistical analyses were performed with R version 4.1.2.

Results

We included 1215 hospitalized patients; of these, 746 (61.4%) were fully vaccinated and 469 (38.6%) were not vaccinated at all. The main characteristics of both the groups are described in Table 1.

Table 1
Characteristics of patients with SARS-CoV-2 (Omicron variant) infection according to vaccine status: demographics, underlying diseases, and presentation

	Vaccinated (N = 746)	Unvaccinated (N = 469)	p
Age (y), n (%)			0.300
<35 y	67 (9.0)	54 (11.5)	
35–65 y	198 (26.5)	128 (27.3)	
>65 y	481 (64.5)	287 (61.2)	
Age (y)	74.0 [57.3–85.0]	71.0 [55.0–83.0]	0.041
Sex: men, n (%)	406 (54.4)	217 (46.3)	0.007
BMI (kg/m ²)	25.9 [22.2–29.4] (n = 391)	26.1 [22.6–29.2] (n = 232)	0.670
Overweight (BMI > 25), n (%)	221 (56.5) (n = 391)	134 (57.8) (n = 232)	0.828
Pre-existing comorbidities, n (%)			
Cardiac failure	121 (23.6) (n = 512)	65 (18.3) (n = 355)	0.073
Respiratory disease	103 (13.8)	47 (10.0)	0.062
Oxygen at home	15 (2.9) (n = 514)	3 (0.8) (n = 354)	0.063
Kidney failure (GFR<30)	88 (12.0) (n = 731)	31 (6.8) (n = 459)	0.004
Diabetes	184 (24.7)	106 (22.7)	0.452
Hypertension	261 (50.8) (n = 514)	183 (51.5) (n = 355)	0.877
Solid cancer for <3 mo	22 (3.0) (n = 745)	9 (1.9)	0.351
Haematologic malignancy	42 (5.6)	10 (2.1) (n = 468)	0.003
Immunodepression ^a	77 (15.0) (n = 514)	33 (9.3) (n = 355)	0.013
At least one comorbidity among the above	523 (70.1)	330 (70.4)	0.949
Number of comorbidities	1.0 [0.0–2.0]	1.0 [0.0–2.0]	0.201
Tobacco, active or discontinued, <3 y, n (%)	44 (11.9) (n = 370)	38 (15.4) (n = 247)	0.258
Previous SARS-CoV-2 infection, n (%)	12 (1.9) (n = 633)	10 (2.4) (n = 415)	0.661
Time from a previous infection (d)	319.0 [43.0–344.0] (n = 9)	215 [97.3–389.5] (n = 10)	0.497
Time from last vaccine dose (d)	113.0 [64.0–178.2]	—	—
Admission for COVID-19	359 (48.7) (n = 737)	317 (69.5) (n = 456)	<0.001
Ct value (lowest value if many)	21.4 [18.2–27.0] (n = 423)	22.1 [19.0–27.3] (n = 273)	0.125
CRP (highest value) (mg/L)	58.0 [21.5–117.5] (n = 575)	66.0 [26.0–126.3] (n = 380)	0.110
The proportion of lungs involved in CT scans, n (%)	n = 179	n = 168	0.003
0–10%	90 (50.3)	51 (30.4)	
11–25%	40 (22.3)	55 (32.7)	
26–50%	32 (17.9)	41 (24.4)	
51–75%	12 (6.7)	18 (10.7)	
>75%	5 (2.8)	3 (1.8)	

Quantitative variables are presented as median (first quartile to third quartile). When data were missing or calculation is performed on a subgroup, the number of patients out of whom the statistic was calculated is mentioned alongside. BMI, body mass index; GFR, glomerular filtration rate; Ct, Cycle threshold; CT, computed tomography; CRP, C-reactive protein.

^a Immunodepression is defined by the presence of one of the following: solid organ transplantation, haematopoietic stem cell transplantation, long-term steroid use, biotherapy, other immunosuppressive therapy, other cause of immunodepression.

Patient included were from Bulgaria (Sofia, n = 43), Croatia (Olsijek, n = 22; Zagreb, n = 132), France (Annecy, n = 368; Paris/Bécélère, n = 169; Caen, n = 131; Grenoble, n = 70; Le Mans, n = 49; Limoges, n = 34; Nantes, n = 40; Poitiers, n = 54), and Turkey (Ankara, n = 77; Karaman, n = 34).

Among vaccinated patients with complete information on their vaccine history (n = 674), most were vaccinated with Pfizer vaccines only (n = 431, 63.9%) or a mix of the two mRNA vaccines (n = 91, 13.5%), whereas a few had received a mix of mRNA and adenovirus vaccines (53, 7.9%) or only Moderna vaccines (n = 52, 7.7%), AstraZeneca vaccines (n = 23, 3.4%) or Janssen vaccines (n = 15, 2.2%). More than half of the vaccinated patients had received more than two doses (373 patients received 3 doses and 22 patients received 4 doses). The median time from the last vaccine dose was 113.0 days (interquartile range, 64.0–178.2).

Characteristics of the SARS-CoV-2 infection according to vaccine status

In bivariate analysis, vaccinated patients were slightly older, more frequently male, and more frequently presented with certain comorbidities (respiratory disease, haematologic malignancy, and immunodepression); however, they did not differ with unvaccinated patients in terms of median number of comorbidities.

Notwithstanding this, unvaccinated patients had more severe SARS-CoV-2 infections (Tables 1 and 2): they were more frequently admitted because of COVID-19 instead of being admitted for another cause with an incident diagnosis of an asymptomatic SARS-

CoV-2 infection (69.5 vs. 48.7%), their lung involvement was more extended on CT scan (69.6 vs. 49.7% had more than 10% of lung involved); they more frequently required oxygen supplementation (64.8 vs. 51.6%) at a higher flow (7 [3.0; 15.0] vs. 4 [2.0; 10.0] L/min) and for a longer duration (7.0 [4.0; 11.8] vs. 5.0 [2.0; 10.0] days), and they more frequently required high-flow oxygen therapy (12.0 vs. 4.4%) and immunomodulatory therapy, such as steroids (58.8 vs. 40.0%) or tocilizumab (6.2 vs. 2.7%). The protective effect of vaccination predominated at an older age (Fig. 1).

Factors associated with severity

Three outcomes were considered: the need to receive oxygen, the need to be admitted to an ICU, and death at day 28. In bivariate analysis, older age, male sex, and most comorbidities (as well as having at least one comorbidity or a higher number of comorbidities) were significantly associated with one or several negative outcomes. Conversely, vaccination was protective against these three outcomes (Table 3).

In multivariate analysis, the protective effect of vaccination persisted with regard to the need for oxygen, need for ICU admission, and risk of death, and it attenuated and practically discarded the negative impact of many comorbidities (Table 4). Older age, solid or haematological cancer, and kidney failure remained independent risk factors for a more severe outcome, notably death. Pulmonary diseases tended to negatively impact the outcome; however, only regarding the need for oxygen was the impact significant.

Table 2
Characteristics of patients with SARS-CoV-2 (Omicron variant) infection according to vaccine status: management and outcomes during hospital stay

	Vaccinated (N = 746)	Unvaccinated (N = 469)	p
Requirement for oxygen, n (%)	385 (51.6)	304 (64.8)	<0.001
Maximal oxygen flow (L/min)	4.0 [2.0–10.0]	7.0 [3.0–15.0]	<0.001
Duration of oxygen therapy (d)	5.0 [2.0–10.0]	7.0 [4.0–11.8]	<0.001
High-flow oxygen, n (%)	32 (4.4) (n = 729)	56 (12.0) (n = 468)	<0.001
Steroid therapy			
Prescribed n (%)	297 (40.0) (n = 743)	275 (58.8) (n = 468)	<0.001
Median Dose (IQR)	7.5 [6.0–11.1] (n = 290)	8.0 [6.0–12.0] (n = 273)	0.009
Duration (d)	5.0 [3.0–10.0] (n = 286)	8.0 [4.0–10.0] (n = 272)	<0.001
Tocilizumab, n (%)	20 (2.7) (n = 745)	29 (6.2)	0.004
Monoclonal Ab, n (%) ^a	30 (4.0) (n = 745)	19 (4.1) (n = 467)	1.000
Antiviral use, n (%) ^b	27 (5.2) (n = 516)	25 (7.0) (n = 355)	0.336
ICU admission, n (%)	60 (8.0)	72 (15.4)	<0.001
ICU duration (d)	7.0 [3.0–15.0]	9.0 [5.0–15.0]	0.095
Invasive mechanical ventilation, n (%)	17 (2.3) (n = 740)	22 (4.7) (n = 464)	0.030
Invasive mechanical ventilation duration (d)	5.0 [2.5–12.5]	8.0 [7.0–20.0]	0.037
Death at day 28, n (%)	71 (9.5)	62 (13.2)	0.044
Death at day 28 and/or ICU admission, n (%)	113 (15.2)	116 (24.7)	<0.001
Length of stay (d)	7.0 [3.0–14.0] (n = 571)	8.0 [4.0–13.0] (n = 377)	0.472

Quantitative variables are presented as median (first quartile to third quartile). When data were missing, the number of patients out of whom the percentage was calculated is mentioned alongside the percentage. Ab, antibody; ICU, intensive care unit; IQR, interquartile range.

^a Among the 30 vaccinated patients who received monoclonal antibodies, 55.6% and 44.4% received tixagevimab/cilgavimab and sotrovimab, respectively. Among the 19 unvaccinated patients, 85.7% and 14.3% received tixagevimab/cilgavimab and sotrovimab, respectively.

^b Among the 27 vaccinated patients who received antiviral, 78.6% received remdesivir and 21.4% favipiravir. Among the 25 unvaccinated patients who received an antiviral, 57.7% received remdesivir and 42.3% received favipiravir.

Table 3
Association of patient characteristics with negative outcomes (bivariate logistic regression)

Factors	Death at day 28		ICU		Oxygen required	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (y)	1.05 [1.04–1.07]	<0.001	1.00 [0.99–1.00]	0.306	1.03 [1.02–1.04]	<0.001
Sex: male	1.14 [0.79–1.64]	0.485	1.48 [1.03–2.14]	0.038	1.38 [1.10–1.73]	0.006
Diabetes mellitus	1.55 [1.04–2.28]	0.028	1.64 [1.10–2.40]	0.014	1.31 [1.00–1.72]	0.048
Hypertension	1.47 [0.97–2.27]	0.073	1.21 [0.80–1.83]	0.365	1.87 [1.43–2.45]	<0.001
Tobacco	1.44 [0.66–2.87]	0.323	1.53 [0.67–3.14]	0.278	1.16 [0.72–1.85]	0.546
BMI (kg/m ²)	0.94 [0.89–0.99]	0.037	1.05 [1.00–1.09]	0.029	1.07 [1.04–1.10]	<0.001
Overweight (BMI > 25)	0.54 [0.30–0.97]	0.040	1.44 [0.83–2.59]	0.207	1.71 [1.24–2.36]	0.001
Kidney failure (GFR < 30)	2.86 [1.77–4.53]	<0.001	2.11 [1.26–3.42]	0.003	1.81 [1.21–2.75]	0.005
Respiratory disease	1.67 [1.01–2.66]	0.036	1.40 [0.83–2.27]	0.189	3.06 [2.06–4.64]	<0.001
Oxygen at home	0.97 [0.15–3.48]	0.968	1.48 [0.34–4.59]	0.539	15.04 [3.07–271.60]	0.009
Cardiac failure	1.71 [1.06–2.69]	0.024	1.39 [0.86–2.19]	0.167	1.58 [1.14–2.22]	0.007
Solid cancer for <3 mo	5.54 [2.56–11.57]	<0.001	0.88 [0.21–2.51]	0.829	1.06 [0.52–2.23]	0.874
Haematologic malignancy	2.29 [1.09–4.42]	0.019	0.49 [0.12–1.36]	0.236	1.34 [0.76–2.43]	0.314
Immunosuppression	1.64 [0.92–2.80]	0.082	1.28 [0.70–2.22]	0.397	1.23 [0.82–1.85]	0.318
At least one comorbidity	1.52 [1.00–2.36]	0.055	1.93 [1.25–3.11]	0.004	1.65 [1.29–2.11]	<0.001
Number of comorbidities	1.26 [1.11–1.42]	<0.001	1.20 [1.06–1.36]	0.003	1.20 [1.10–1.30]	<0.001
Previous SARS-CoV-2 infection	0.40 [0.05–2.98]	0.368	0.42 [0.06–3.17]	0.402	0.81 [0.35–1.90]	0.630
Time from the last infection (d) ^a		1.000		0.997		0.739
Vaccination	0.69 [0.48–0.99]	0.045	0.48 [0.33–0.69]	<0.001	0.58 [0.46–0.73]	<0.001
Time from last vaccine injection (d) ^a		0.289		0.117		0.104

BMI, body mass index; GFR, glomerular filtration rate; ICU, intensive care unit.

^a For the time from the last infection and from the last vaccine injection, the scarcity of data made the calculation of CIs irrelevant.

Influence of the VOC (Delta vs. Omicron)

Patients infected by the Omicron VOC presented less severe infection, either vaccinated or unvaccinated, compared with patients infected by the Delta VOC.

In bivariate analysis (Tables 5 and 6), whether vaccinated or not, Omicron-infected patients were significantly (or at least presented a trend) less hospitalized for COVID-19 (significantly among those vaccinated); had lower median C-reactive protein (CRP) (significantly among those vaccinated); had less extended lung lesion on CT scan (significantly among those unvaccinated); less frequently required oxygen supplementation, high-flow oxygen therapy, steroid therapy, or tocilizumab (significantly among both vaccinated

and unvaccinated); less frequently required to be admitted in ICU (both vaccinated and unvaccinated); and had lower 28-day mortality (among those vaccinated).

In multivariate analysis (Table 7), Omicron infection, compared with Delta, was associated with less need for oxygen therapy, less ICU admission, and fewer deaths, whereas vaccination and a history of SARS-CoV-2 infection were also protective. Only male sex, older age, kidney failure, immunosuppression, and solid cancer were still risk factors for mortality.

Interactions suggest that the benefit of vaccination is lesser on the protective effect on ICU need among immunosuppressed patients and among patients with a history of SARS-CoV-2 infection.

Table 4
Factors associated with negative outcomes, with a multivariate logistic regression (best model according to Akaike Information Criteria (AIC))

	Death on day 28		ICU		Need for oxygen	
	Best model	p	Best model	p	Best model	p
Age	1.06 [1.04-1.08]	<0.001			1.03 [1.02-1.03]	<0.001
Sex: male			1.25 [0.82-1.90]	0.304	1.37 [1.02-1.83]	0.036
Diabetes			1.51 [0.95-2.36]	0.076		
Kidney failure	2.52 [1.44-4.31]	0.001	2.30 [1.29-3.97]	0.004		
Previous SARS-CoV-2 infection	0.29 [0.02-1.59]	0.247	0.36 [0.02-1.81]	0.325		
Vaccination	0.50 [0.32-0.77]	0.002	0.40 [0.26-0.62]	<0.001	0.34 [0.25-0.46]	<0.001
Pulmonary diseases	1.51 [0.86-2.56]	0.138	1.68 [0.96-2.85]	0.060	1.91 [1.19-3.12]	0.009
O ₂ at home					8.41 [1.58-156.23]	0.044
Solid cancer for <3 mo	7.99 [2.97-20.80]	<0.001				
Haematological cancer	3.84 [1.67-8.29]	0.001				
Immunosuppressed					1.58 [1.03-2.46]	0.038

Models were explored with a full model including the variable 'gender', 'Age', 'Diabetes', 'Hypertension (HTA)', 'KidneyFailure', 'O₂_home', 'CardiacFailure', 'ImmunoSup', 'previousSARS-CoV-2 infection', 'Vaccination', 'PulmDis', 'SolidCancer3M', 'HematoK', and 'OneComorb'. 'Tobacco', 'BMI', and 'overweight' were not included owing to more than 50% of missing data. No interactions were found. ICU, intensive care unit.

Discussion

Despite the fact that Omicron emerged as a new VOC at the end of 2021, our results show that vaccines designed in early 2020 still protect from severe forms. This protection persists even in older patients and patients with comorbidities and prevails regardless of whether the VOC is a Delta or Omicron. However, greater age, kidney failure, and solid or haematological cancer are still associated with mortality.

The large cohort of 2167 patients obtained by merging our two cohorts not only highlights the fact that the VOC is a risk factor in itself, independent from the known risk factors and vaccine status, with a greater risk of severe form associated with Delta rather than Omicron, but also highlights the impact of a history of SARS-CoV-2 infection. Indeed, the whole cohort provided sufficient power to show a significant influence of a past SARS-CoV-2 infection regarding mortality, need for ICU, or need for oxygen. For the Delta-only cohort, patients with a previous SARS-CoV-2 infection less frequently needed oxygen or ICU but only with a non-significant trend towards lower mortality [7]. A non-significant but likewise trend (for the three outcomes) was observed in the current study on Omicron. The fact that a prior infection is selected by the model suggests its importance; however, the lack of significance also suggests either a lack of power or a lesser importance compared with vaccination in protecting the patient. Consequently, immunity resulting from a prior infection may not be regarded as necessarily better or sufficient compared with vaccine-induced immunity. Another explanation could be that the antigenic distance between Omicron and the previous variants may decrease the protection provided by the Omicron infection as compared with a Delta infection.

Our results regarding the positive impact of vaccination on the SARS-CoV-2 infection are in line both with previous studies on previous variants (particularly Delta [7,10,11]) and Omicron [10,12]. Some of these studies evidenced a marked decrease in vaccine efficacy towards SARS-CoV-2 infection but conserved efficacy regarding severe infection and death. Most of the studies included patients even if they were not hospitalized; the fact that we observed this protection even among patients hospitalized for COVID-19 (compared with those with an incidental SARS-CoV-2 infection with no clinical COVID-19) is a strong argument confirming the benefits of the vaccine.

Our observation regarding the lower risk of severe forms of Omicron infection compared with Delta is in accordance with the current literature. Indeed, previous studies concluded that Omicron was associated with less severe infections [4,13]. However, these

studies were carried out at the population level, where a large number of asymptomatic or mild cases could have gone undetected, thereby diluting the power to detect severe cases. Moreover, Delta and Omicron waves were not contemporaneous and have spread in potentially very different populations in terms of vaccine coverage, history of SARS-CoV-2 infection, etc. Such differences in the populations could generate differences misattributed to the virus. However, with a multivariate analysis applied to two cohorts with the same design, our study was able to decouple the effect of Omicron from vaccination and consequently confirmed that it produces less severe forms than Delta. Nonetheless, the lesser proportion of severe forms with Omicron compared with Delta is not as marked among older people compared with the general population [6]. It could be related to the difference of age between the Delta and the Omicron cohort but only partially because the multivariate analysis showed an effect independent between age and VOC. Consequently, severe forms do exist with Omicron and are not negligible.

Our study presents some limitations, in particular missing data, mostly because of its retrospective design; for that reason, some items were not taken into consideration in the analysis, such as vaccine type. Moreover, we included patients from four countries, and our results may have been different if more countries (either European or not) had been represented. In addition, we did not perform anti-Spike serology at admission; anti-Spike antibody level has been shown to be associated with prognosis [14,15], and it might have facilitated understanding of the severity of SARS-CoV-2 infection in some vaccinated subjects, in particular among immunosuppressed subjects who could present a lesser response to vaccines. In addition, the availability of antiviral treatment was not comparable between the Delta and the Omicron wave, which could have had an impact on mortality.

The main strength of our study is the large number of highly phenotyped patients, making our conclusions probably valid for most populations. In particular, vaccine status was individually checked, ensuring accurate classification of patients. In addition, the inclusion period we chose corresponds to a phase of homogeneous circulation of a unique variant, ensuring more precision to our conclusions. Lastly, the fact that the data collection was aligned with the Delta study performed in 2021 enabled us to conduct the comparison between the two variants with high validity.

Our study has several implications. Despite the immune escape by Omicron, vaccination with the currently available vaccines still retains efficacy against severe infections, even among older patients or those with comorbidities, which is an important rationale for vaccine campaigns to be remembered. It also questions the

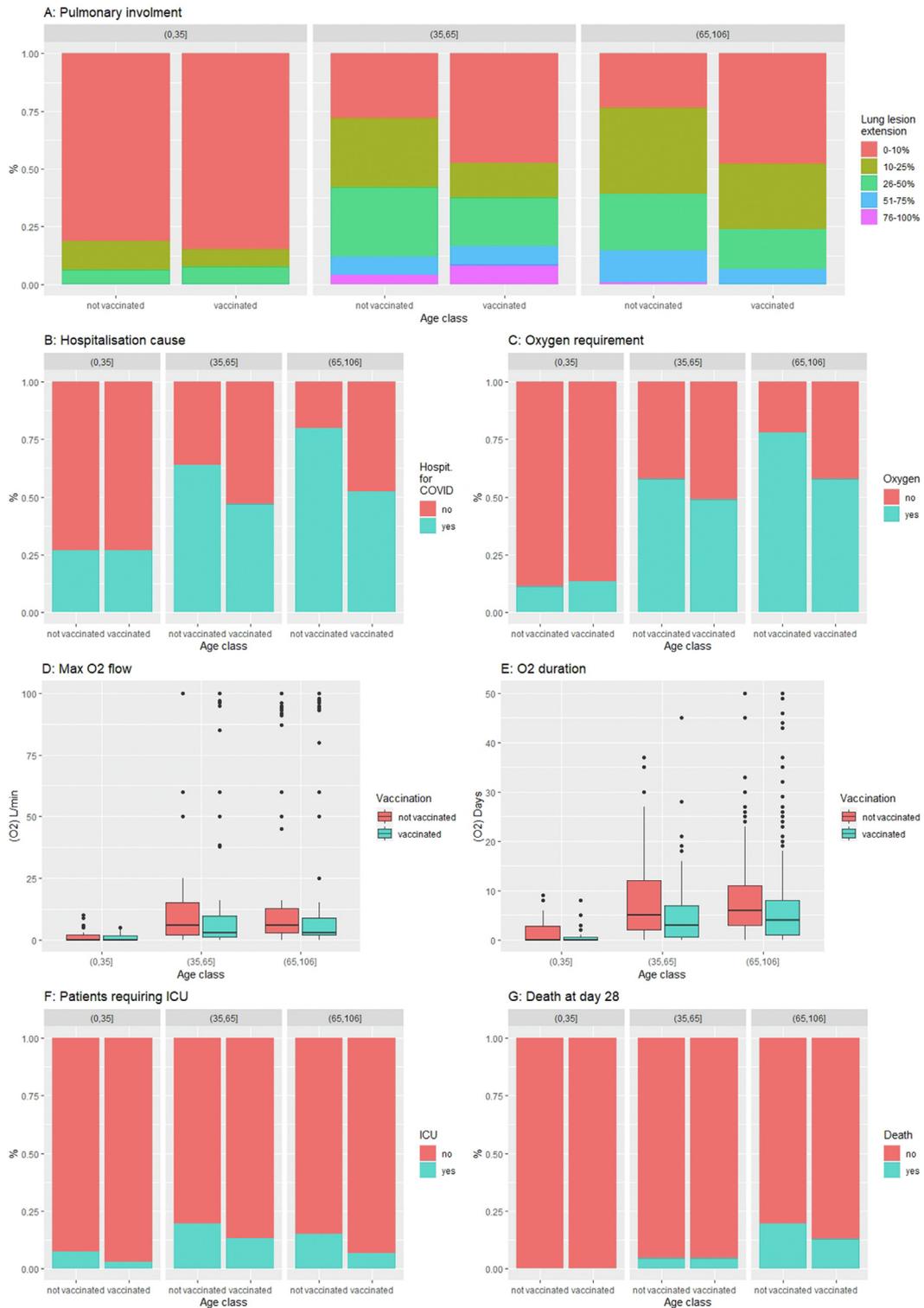


Fig. 1. SARS-CoV-2 (Omicron variant) infection severity criteria according to vaccine status in the three age classes. (a) Extension of lung lesions on computed tomography scanner; (b) hospitalization cause; (c) proportion of patients requiring oxygen; (d) maximal oxygen flow; (e) duration of oxygen therapy; (f) proportion of patients requiring intensive care unit (ICU); (g) proportion of death at day 28.

necessity of booster doses, as in haemodialysis patients for whom vaccine-induced protection is proportional to the number of doses [16,17].

Omicron is less associated with severe COVID-19 but is more contagious than Delta [2,3]; this explains why a significant number

of deaths were still observed during the BA-1 and BA-2 waves [18], the low frequency of severe form being counterbalanced by the massive number of infections. This observation undermines the statements describing Omicron as a step of SARS-CoV-2 towards a more 'banal' coronavirus [19–21], such as 229E, NL63, OC43, and

Table 5
Comparison of the Omicron infection with the Delta infection according to vaccination status: demographics, underlying diseases, and presentation

	Vaccinated (N = 1220)		p	Unvaccinated (N = 950)		p
	Omicron (n = 746)	Delta (n = 474)		Omicron (n = 469)	Delta (n = 481)	
Age (y), n (%)			0.031			<0.001
<35 y	67 (9.0)	27 (5.7)		54 (11.6)	97 (20.2)	
35–65 y	198 (26.6)	111 (23.4)		128 (27.4)	225 (46.8)	
>65 y	481 (64.5)	336 (70.9)		287 (61.2)	159 (33.1)	
Age (y)	74.0 [57.3–85.0]	75.0 [63.3–84.0]	0.012	71.0 [55.0–83.0]	55.0 [38.0–73.0]	<0.001
Sex: men, n (%)	406 (54.4)	261 (55.1)	0.873	217 (46.3)	223 (46.4)	1.000
BMI (kg/m ²)	25.9 [22.2–29.4]	25.8 [22.3–31.1]	0.036	26.1 [22.6–29.2]	27.2 [24.2–31.2]	<0.001
Overweight (BMI > 25), n (%)	221 (56.5)	192 (56.6)	1.000	134 (57.8)	222 (69.4)	0.006
Pre-existing comorbidities, n (%)						
Cardiac failure	121 (23.6)	50 (13.7)	<0.001	65 (18.3)	29 (8.0)	<0.001
Respiratory disease	103 (13.8)	91 (20.7)	0.002	47 (10.0)	54 (12.6)	0.256
Oxygen at home	15 (2.9)	14 (4.0)	0.515	3 (0.8)	5 (1.4)	0.501
Kidney failure (GFR < 30)	88 (12.0)	51 (15.2)	0.182	31 (6.8)	10 (3.2)	0.041
Diabetes	184 (24.7)	127 (28.7)	0.141	106 (22.6)	76 (17.8)	0.086
Hypertension	261 (50.8)	244 (55.1)	0.206	183 (51.5)	123 (28.7)	<0.001
Solid cancer for <3 mo	22 (3.0)	17 (4.8)	0.170	9 (1.9)	8 (2.2)	0.945
Haematologic malignancy	42 (5.6)	25 (7.1)	0.428	10 (2.1)	6 (1.7)	0.869
Immunodepression	77 (15.0)	74 (20.3)	0.048	33 (9.3)	21 (5.8)	0.110
At least one comorbidity among those above	523 (70.1)	369 (90.4)	<0.001	330 (70.4)	306 (86.9)	<0.001
Number of comorbidities	1.0 [0.0–2.0]	2.0 [1.0–3.0]	<0.001	1.0 [0.0–2.0]	1.0 [0.0–2.0]	0.010
Tobacco, active or discontinued < 3 y, n (%)	44 (11.9)	36 (10.3)	0.580	38 (15.4)	49 (14.3)	0.800
Previous SARS-CoV-2 infection, n (%)	12 (1.9)	19 (5.4)	0.005	10 (2.4)	12 (3.4)	0.533
Time from a previous infection (d)	319.0 [43.0–344.0]	226.0 [176.5–299.0]	0.688	215.0 [97.3–389.5]	69 [43.3–244.3]	0.113
Time from last vaccine dose (d) ^a	113.0 [64.0–178.2]	125.0 [82.0–166.5]	0.716	–	–	–
Admission for COVID-19	359 (48.7)	281 (59.3)	<0.001	317 (69.5)	361 (75.1)	0.069
Ct value (lowest value if many)	21.4 [18.2–27.0]	26.0 [18.0–34.0]	<0.001	22.1 [19.0–27.3]	26.0 [21.0–33.0]	<0.001
CRP (highest value) (mg/L)	58.0 [21.5–117.5]	87.5 [31.3–152.8]	<0.001	66.0 [26.0–126.3]	86.0 [34.0–145.0]	0.073
The proportion of lungs involved on CT scan n (%)			0.134			<0.001
0–10%	90 (50.3)	67 (36.8)		51 (30.4)	31 (13.5)	
11–25%	40 (22.3)	50 (27.5)		55 (32.7)	57 (24.9)	
26–50%	32 (17.9)	39 (21.4)		41 (24.4)	75 (32.8)	
51–75%	12 (6.7)	18 (9.9)		18 (10.7)	49 (21.4)	
>75%	5 (2.8)	8 (4.4)		3 (1.8)	17 (7.4)	

BMI, body mass index; GFR, glomerular filtration rate; Ct, Cycle threshold; CT, computed tomography; CRP, C-reactive protein.

^a For the time from the last infection and from the last vaccine injection.

Table 6
Comparison of the Omicron infection with the Delta infection according to vaccine status: management and outcomes during hospital stay

	Vaccinated (N = 1220)		p	Unvaccinated (N = 950)		p
	Omicron (n = 746)	Delta (n = 474)		Omicron (n = 469)	Delta (n = 481)	
Requirement for oxygen, n (%)	385 (51.6)	229 (57.5)	0.064	304 (64.8)	270 (73.0)	0.014
Maximal oxygen therapy (L/min)	3.0 [1.0–9.0]	3.0 [0.0–8.8]	0.140	6.0 [2.0–15.0]	6.0 [2.0–50.0]	0.153
Duration of oxygen therapy (d)	3.0 [0.5–7.3]	3.0 [0.0–8.0]	0.369	6.0 [2.0–10.0]	6.0 [2.0–12.0]	0.629
High-flow oxygen, n (%)	32 (4.4)	49 (13.6)	<0.001	56 (12.0)	105 (29.4)	<0.001
Steroid therapy						
Prescribed, n (%)	297 (40.0)	174 (47.2)	0.027	275 (58.8)	250 (68.5)	0.005
Median dose (IQR)	7.5 [6.0–10.7]	6.0 [6.0–7.5]	<0.001	8.0 [6.0–12.0]	6.0 [6.0–9.0]	<0.001
Duration (d)	5.0 [3.0–10.0]	9.0 [5.0–10.0]	<0.001	8.0 [4.0–10.0]	10.0 [7.0–10.0]	<0.001
Tocilizumab, n (%)	20 (2.7)	21 (6.3)	0.007	29 (6.2)	59 (18.3)	<0.001
Monoclonal Ab, n (%)	30 (4.0)	27 (7.3)	0.030	19 (4.1)	7 (1.9)	0.122
ICU admission, n (%)	60 (8.0)	60 (16.2)	<0.001	72 (15.4)	133 (36.0)	<0.001
Invasive mechanical ventilation, n (%)	17 (2.3)	25 (6.9)	<0.001	22 (4.7)	59 (16.5)	<0.001
Death at day 28, n (%)	71 (9.5)	74 (16.7)	<0.001	62 (13.2)	53 (12.2)	0.733
Death at day 28 and/or ICU admission, n (%)	113 (15.1)	116 (30.7)	<0.001	116 (24.7)	166 (44.6)	<0.001
Length of stay	7.0 [3.0–14.0]	9.0 [4.0–16.0]	0.003	8.0 [4.0–13.0]	7.0 [3.0–15.0]	0.866

ICU, intensive care unit; IQR, interquartile range; Ab, Antibody.

HKU1, and is an argument to maintain high vaccine coverage. Moreover, bivalent mRNA vaccines have received market authorization from the European Medicines Agency ([22] for Wuhan SARS-CoV-2 and Omicron BA.1 SARS-CoV-2), and from the U.S. Food and Drug Administration ([23] Wuhan SARS-CoV-2 and Omicron BA.4/5); our results suggest that patients with risk factors for severe COVID-19 should not wait for such vaccines before receiving a boosting injection (such an injection being recommended

3–6 months after the previous one), as currently available vaccines still retain efficacy.

During the second quarter of 2022, new Omicron subvariants, BA.4 and BA.5, progressively became predominant in Europe. Studies showed a decrease in the neutralization activities of antibodies elicited by vaccination [24] and of therapeutic monoclonal antibodies [25] towards them. New studies are needed to determine the extent to which vaccination status, the number of vaccine

Table 7
Multivariate analysis on the merged cohort (Delta + Omicron)

	Death on day 28		ICU		Need for oxygen	
	Best model	p	Best model	p	Best model	p
Variant: Omicron	0.53 [0.37–0.76]	0.001	0.19 [0.12–0.28]	<0.001	0.50 [0.38–0.67]	<0.001
Sex: male	1.66 [1.15–2.41]	0.007	1.37 [0.96–1.95]	0.084	1.65 [1.25–2.18]	<0.001
Age	1.07 [1.05–1.08]	<0.001			1.04 [1.03–1.04]	<0.001
Kidney failure	2.32 [1.46–3.67]	<0.001	0.41 [0.15–0.93]	0.050		
HTA	1.28 [0.87–1.90]	0.211				
Immunosuppressed	2.21 [1.30–3.66]	0.003	0.79 [0.31–1.83]	0.593	1.56 [1.05–2.33]	0.028
Previous SARS-CoV-2 infection	0.14 [0.01–0.67]	0.053	0.10 [0.01–0.50]	0.028	0.08 [0.02–0.26]	<0.001
Vaccination	0.45 [0.30–0.66]	<0.001	0.26 [0.17–0.39]	<0.001	0.20 [0.14–0.28]	<0.001
Solid cancer for <3 mo	5.61 [2.53–12.57]	<0.001	0.41 [0.09–1.31]	0.174		
Overweight			1.72 [1.10–2.77]	0.021	1.63 [1.17–2.27]	0.004
At least one comorbidity			1.68 [0.84–3.45]	0.146	1.61 [0.97–2.67]	0.064
O ₂ treatment at home					2.86 [1.05–9.28]	0.053
Interaction vaccination × immunosuppressed ^a			2.95 [1.03–8.87]	0.047		
Interaction vaccination × previous COVID-19 ^b					5.60 [1.21–28.49]	0.030

^a In the model for ICU, a significant and positive interaction was found between being vaccinated and being immunosuppressed, which means that the protective effect of vaccination on the risk of ICU admission decreases among immunosuppressed patients.

^b In the model for O₂ need, a significant and positive interaction was found between being vaccinated and having a previous SARS-CoV-2 infection, which means that the effect of vaccination was decreased among patients having previously had SARS-CoV-2 infection. In addition, a trend towards the interaction between being vaccinated and being immunosuppressed was found, similar to the ICU model, but was not significant (p 0.08), which suggests an effect comparable to the ICU model. ICU, intensive care unit; HTA, Hypertension.

doses, and the timing of the last injection bring protection against severe infections in addition to the impact of the divalent vaccines.

Author contributions

GB and OE conceptualized the study, developed the methodology, and performed the software analysis. SA, NT, JFF, JM, ML, PV, CJ, and RC performed the validation. GB and OE performed the formal analysis. GB, SA, NT, JM, JFF, SB, ML, PV, RC, MD, CJ, and OE performed the investigation. All authors curated the data. GB and OE wrote the original draft of the manuscript. SA, ML, NT, PV, JFF, JM, SB, CJ reviewed and edited the manuscript. GB and OE visualized the data. GB and OE supervised the study. GB and OE performed the administration.

Transparency declaration

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Appendix A. Supplementary data

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