



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

## Clinical Microbiology and Infection

journal homepage: [www.clinicalmicrobiologyandinfection.com](http://www.clinicalmicrobiologyandinfection.com)

## Original Article

## Impact of vaccination on the symptoms of hospitalised patients with SARS-CoV-2 Delta variant (B.1.617.1) infection

Olivier Epaulard<sup>1, 2, 3, \*</sup>, Sophie Abgrall<sup>3, 4</sup>, Maeva Lefebvre<sup>3, 5</sup>, Jean-François Faucher<sup>3, 6, 7</sup>, Jocelyn Michon<sup>3, 8</sup>, Emilia Frentiu<sup>3, 9</sup>, Sophie Blanchi<sup>3, 10</sup>, Cécile Janssen<sup>3, 11</sup>, Gabrielle Charbonnier<sup>3, 12</sup>, Audrey Fresse<sup>3, 13</sup>, Simon Laurent<sup>3, 14</sup>, Lena Sandjakian<sup>3, 15</sup>, Pierre Casez<sup>3, 16</sup>, Aba Mahamat<sup>3, 17</sup>, Guillaume Beraud<sup>3, 18</sup>

<sup>1</sup> Infectious Diseases, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France

<sup>2</sup> Groupe de Recherche en Infectiologie Clinique, CIC, 1406, Inserm-CHUGA-UGA, Grenoble, France

<sup>3</sup> Groupe Vaccination-Prévention de La Société de Pathologie Infectieuse de Langue Française (SPILF), France

<sup>4</sup> APHP, Hôpital Antoine Béclère, Service de Médecine Interne, Clamart, Université Paris-Saclay, UVSQ, INSERM U1018, CESP, Le Kremlin-Bicêtre, France

<sup>5</sup> Infectious Diseases Department, Centre for Prevention of Infectious and Transmissible Diseases, CHU Nantes and INSERM UIC 1413 Nantes University, Nantes, France

<sup>6</sup> CHU Limoges, Department of Infectious Diseases and Tropical Medicine, Limoges, France

<sup>7</sup> Inserm U1094, IRD U270, Univ. Limoges, CHU Limoges, EpiMaCT, France

<sup>8</sup> Department of Infectious Diseases, University Hospital of Caen, Caen, France

<sup>9</sup> Infectious Diseases Department, Centre Hospitalier Universitaire de Nancy, Nancy, France

<sup>10</sup> Infectious Diseases Department, Centre Hospitalier, Le Mans, France

<sup>11</sup> Infectious Disease Unit, Centre Hospitalier Annecy Genevois, Annecy, France

<sup>12</sup> Infectious Diseases Department, Centre Hospitalier Universitaire Grenoble-Alpes, Grenoble, France

<sup>13</sup> Pharmacovigilance, Centre Hospitalier Universitaire de Nancy, Nancy, France

<sup>14</sup> Department of Infectious Diseases, University Hospital of Caen, Caen, France

<sup>15</sup> CHU Limoges, Department of Infectious Diseases and Tropical Medicine, Limoges, France

<sup>16</sup> Infectious Disease Unit, Centre Hospitalier Annecy Genevois, Annecy, France

<sup>17</sup> Regional Centre for Prevention of Infectious Diseases and Healthcare-Associated Infections, General Hospital of Ajaccio, Ajaccio, France

<sup>18</sup> Department of Internal Medicine and Infectious Diseases, University Hospital of Poitiers; Poitiers, France

## ARTICLE INFO

## Article history:

Received 20 February 2022

Received in revised form

6 June 2022

Accepted 16 June 2022

Available online xxx

Editor: L. Leibovici

## Keywords:

Breakthrough infection

Delta

SARS-CoV-2

Severity

Vaccine

## ABSTRACT

**Objectives:** The diffusion of the SARS-CoV-2 Delta (B.1.617.2) variant and the waning of immune response after primary Covid-19 vaccination favoured the breakthrough SARS-CoV-2 infections in vaccinated subjects. To assess the impact of vaccination, we determined the severity of infection in hospitalised patients according to vaccine status.

**Methods:** We performed a retrospective observational study on patients hospitalised in 10 centres with a SARS-CoV-2 infection (Delta variant) from July to November 2021 by including all patients who had completed their primary vaccination at least 14 days before hospital admission and the same number of completely unvaccinated patients. We assessed the impact of vaccination and other risk factors through logistic regression.

**Results:** We included 955 patients (474 vaccinated and 481 unvaccinated). Vaccinated patients were significantly older (75.0 [63.25-84.0] vs. 55.0 [38.0-73.0];  $p < 0.001$ ), more frequently males (55.1% (261/474) vs. 46.4% (223/481);  $p = 0.009$ ), and had more comorbidities (2.0 [1.0-3.0] vs. 1.0 [0.0-2.0];  $p < 0.001$ ). Vaccinated patients were less often admitted for Covid-19 (59.3% (281/474) vs. 75.1% (361/481);  $p < 0.001$ ), had less extended lung lesions ( $\leq 25\%$ : 64.3% (117/182) vs. 38.4% (88/229);  $p < 0.001$ ), required oxygen less frequently (57.5% (229/398) vs. 73.0% (270/370);  $p < 0.001$ ), at a lower flow (3.0 [0.0-8.7] vs. 6.0 [2.0-50.0] L/min,  $p < 0.001$ ), and for a shorter duration (3 [0.0-8.0] vs. 6 [2.0-12.0] days,  $p < 0.001$ ), and required less frequently intensive care unit admission (16.2% (60/370) vs. 36.0% (133/369);  $p < 0.001$ ) but had comparable mortality in bivariate analysis (16.7% (74/443) vs. 12.2% (53/433);  $p = 0.075$ ). Multivariate logistic regression showed that vaccination significantly decreased the risk of

\* Corresponding author. Olivier Epaulard, Service des Maladies Infectieuses, CHU Grenoble Alpes, CS10217, 38043, Grenoble, cedex 09, France

E-mail address: [oeaulard@chu-grenoble.fr](mailto:oeaulard@chu-grenoble.fr) (O. Epaulard).

death (0.38 [0.20–0.70]( $p = 0.002$ ), ICU admission (0.31 [0.21–0.47]( $p < 0.001$ ) and oxygen requirement (0.16 [0.10–0.26]( $p < 0.001$ ), even among older patients or with comorbidities.

**Conclusions:** Among patients hospitalised with a delta variant SARS-CoV-2 infection, vaccination was associated with less severe forms, even in the presence of comorbidities. **Olivier Epaulard, Clin Microbiol Infect 2022;•:1**

© 2022 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

## Introduction

Despite reaching relatively high coronavirus disease 2019 (Covid-19) vaccine coverage, during the second half of 2021 many countries (notably in Europe and North America areas) faced a new wave of SARS-CoV-2 infections. This may be related to a variable proportion of the population being not immunised yet, anti-Spike antibody levels decrease over time after two doses of either RNA or ChAdOx1-S vaccines [1], and vaccination being less efficient against the Delta (B.1.617.2) variant of concern (VOC), which became the virtually single circulating form of SARS-CoV-2 during early summer 2021, compared to the original strain [2]. Several studies have characterised the rate of such breakthrough infections in vaccinated persons [3], and reported that this risk increased over time after primary vaccination [4]. Even with the Delta variant, the rate of Covid-19-related hospitalisations [5], intensive care unit (ICU) admissions, and mortality [6] were much lower in those who received two doses of the aforementioned vaccines.

Nevertheless, no precise data are currently available regarding the characteristics of vaccinated patients hospitalised with a SARS-CoV-2 infection. We therefore aimed to determine whether vaccination, among other factors, influenced the outcome of hospitalised patients with a SARS-CoV-2 infection, in particular in terms of need for oxygen, ICU admission, and death within 28 days after hospitalisation.

## Methods

### Population

We conducted a retrospective, multicentre study across 10 hospitals in France (Ajaccio, Annecy, Caen, Clamart, Grenoble, Le Mans, Limoges, Nancy, Nantes and Poitiers). These centres differed by size (from 330 to 2100 beds) and by specialisation (7 being tertiary, university hospitals); all had intensive care units, and an infectious disease unit. Hospitalised patients with a polymerase chain reaction (PCR)-proven SARS-CoV-2 infection from July to November 2021, i.e., when the Delta variant was virtually the only circulating SARS-CoV-2 variant in France, either at the time of admission or after admission, were selected. Among them, two populations were identified and included in the study:

- All patients who had received at least either one injection of the Ad26. CoV2–S vaccine (Janssen) (at least 14 days before date of PCR) or two injections of the ChAdOx1-S vaccine (AstraZeneca) and/or RNA vaccines (tozinameran [Pfizer/BioNTech] and elasmóran [Moderna]) (with the second dose given at least 14 days before date of PCR);
- the equivalent number of patients without any vaccination before hospital admission. This last group was composed by including for each study month and in each hospital as many unvaccinated patients as vaccinated patients, by chronological order of hospitalisation.

All the centres screened their patients to include only the Delta variant. For one centre, the inclusion was prolonged up to the December 13th, but mutation screening (by multiplex RT-qPCR targeting a set of predefined mutations) guaranteed that only the delta variant was involved. The following data were collected: year of birth, gender, and pre-existing comorbidities (respiratory disease, cardiac failure, arterial hypertension, solid tumour, haematological neoplasia, and kidney failure, which was determined by the Cockcroft formula based on data collected at hospital admission); Covid-19 vaccination history; clinical data at admission and minimum cycle threshold (Ct) PCR level (the number of amplification cycles required for the signal to cross the threshold; Ct number is inversely correlated with the amount of target nucleic acid in the sample); maximum C-reactive protein plasmatic level; extension of lung disease on computed tomography (CT-scan (if performed)); need for oxygen with duration and maximal flow; need for high-flow oxygen therapy; need for ICU admission; need for invasive mechanical ventilation; prescription of steroid, tocilizumab, and/or monoclonal antibodies; and mortality at day 28.

According to the French law on ethics, patients were informed during their hospital stay that their anonymised medical data could be used for research purposes; they were given the possibility to refuse this usage. As requested by French ethics and regulatory laws, the ethical committee of the French-speaking Society of Infectious Diseases (SPIIF) (IRB00011642) gave its approval for the study (N°2022-0101), and the study was declared to the French National Commission for Informatics and Liberties (CNIL MR004: n°2,224,742).

### Statistical analysis

Firstly, a descriptive analysis was performed in the cohort population according to vaccination status. Qualitative variables were described as counts (percentage) and frequency distributions were compared with the Chi square test or Fisher's exact test when appropriate. Continuous variables were expressed as median (1<sup>st</sup> quartile; 3rd quartile) and differences were tested with the independent t-test for normally distributed variables or otherwise the Mann-Whitney U test. Secondly, univariate and multivariate logistic regressions based on general linear models were performed with a stepwise variable selection according to the Akaike Information Criterion (AIC) [7]. Factors associated with severe forms of infection defined by three outcomes, namely requirement for oxygen, ICU admission and death at day 28, were assessed, focusing on the impact of vaccination. To assess the impact of comorbidities and vaccination, we selected all the potential risk factors for severe outcome presented in Table 2 for the multivariate model (Table 3 and supplementary Table 1). Only the best models (according to AIC) are presented in Table 3, therefore variables that are both non-significantly associated with the outcome and not informative for the model are not excluded. In addition, to manage Missing data Not At Random (MNAR), multivariate analysis was initially performed only on the dataset with complete cases, after which the model was applied to the full dataset [8]. Results are presented

**Table 1**  
Characteristics of patients with SARS-CoV-2 infection according to vaccinal status: Demographics, underlying diseases and presentation

	Vaccinated (N = 474)	Unvaccinated (N = 481)	p-value
Age (years)*	75.0 [63.25-84.0]	55.0 [38.0-73.0]	<0.001
Age (years) n (%)			<0.001
<35y	27 (5.70)	97 (20.17)	
35-65y	111 (23.42)	225 (46.78)	
>65y	336 (70.89)	159 (33.06)	
Gender: men n (%)	261 (55.06)	223 (46.36)	0.009
Body Mass Index (kg/m <sup>2</sup> )*	25.76 [22.32-31.14] (N=338)	27.20 [24.15-31.22] (N=320)	0.051
Overweight (BMI>25) n (%)	192 (56.64) (N=339)	222 (69.38) (N=320)	<0.001
Pre-existing comorbidities n (%)			
Cardiac failure	50 (13.66) (N=366)	29 (7.99) (N=363)	0.020
Respiratory disease	91 (20.73) (N=439)	54 (12.65) (N=427)	0.002
Oxygen at home)	14 (3.97) (N=353)	5 (1.45) (N=346)	0.070
Kidney failure (GFR<30)	51 (15.22) (N=335)	10 (3.15) (N=317)	<0.001
Diabetes	127 (28.73) (N=442)	76 (17.76) (N=428)	<0.001
Hypertension	244 (55.08) (N=443)	123 (28.74) (N=428)	<0.001
Solid cancer (under treatment or for less than 3 months)	17 (4.80) (N=354)	8 (2.23) (N=358)	0.070
Hematologic malignancy	25 (7.06) (N=354)	6 (1.72) (N=348)	<0.001
Immunodepression	74 (20.33) (N=364)	21 (5.85) (N=359)	<0.001
At least one comorbidity among those above	369 (90.44) (N=408)	306 (86.93) (N=352)	0.135
Number of comorbidities*	2.0 [1.0-3.0]	1.0 [0.0-2.0]	<0.001
Tobacco, active or discontinued <3 years, n (%)	36 (10.32) (N=349)	49 (14.29) (N=343)	0.140
Previous COVID infection n (%)	20 (5.62) (N=354)	13 (3.70) (N=350)	0.285
Time from a previous infection (days)*	226 [176.5-299.0] (n=14)	69 [43.3-244.3] (n=12)	0.076
Time from last vaccine dose (days)*	125 [82.0-166.5] (N=439)	..	
Admission for Covid-19 (out of 955)	281 (59.28)	361 (75.05)	<0.001
Ct (lowest value if many)	26.0 [18.0-34.0] (N=251)	26.0 [21.0-33.0] (N=201)	0.741
CRP (highest value) (mg/L)*	87.50 [31.25-152.75] (N=350)	86.0 [34.0-145.0] (N=337)	0.682
Proportion of involved lung tissue in CT scanner n (%)	N=182	N=229	<0.001
0-10%	67 (36.81)	31 (13.54)	
11-25%	50 (27.47)	57 (24.89)	
26-50%	39 (21.43)	75 (32.75)	
51-75%	18 (9.89)	49 (21.40)	
>75%	8 (4.40)	17 (7.42)	

Quantitative variables, identified with \* are presented as median (1<sup>st</sup> quartile - 3rd quartile). When data were missing the number of patients out of which the percentage was calculated is mentioned alongside the percentage.

based on the full dataset, as they were similar to the analysis restricted to the complete case dataset. Finally, a multivariate analysis was similarly carried out on the dataset of vaccinated patients only, so as 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. All statistical analyses were performed with R version 4.1.2. Packages readxl, Amelia, xlsx, ggplot2, MASS, VIM, ggpubr were used.

## Results

### Population

Nine hundred seventy-four patients were initially included; 19 were excluded for i) being under 18 years (n = 4), ii) not being fully vaccinated (n = 12) or iii) being infected with a VOC other than Delta or hospitalised when delta variant was not the only circulating variant (n = 3). The characteristics of the 955 patients finally included, among whom 474 were vaccinated and 481 were not, are detailed in Table 1.

The two groups differed on several points: vaccinated patients were significantly older and had more comorbidities (reflecting the sequential prioritisation of the vaccine campaign during the early months of 2021), although they also had a lower body mass index. Among vaccinated patients, the median delay since the most recent dose was 125 days. The tozinameran (Pfizer/BioNTech) vaccine had been used in 357 (76.1%) patients. ChAdOx1-S (Astra-Zeneca), Ad26. CoV2-S (Janssen), and elasméran (Moderna) had been used in 62 (13.2%), 27 (5.8%), 23 (4.9%) patients respectively.

### Severity of the SARS-CoV-2 infection

All in all, vaccinated patients had milder forms of SARS-CoV-2 infection (Table 2). They were less frequently hospitalised because of the infection itself; they had less extended lung lesions on CT-scan; they required oxygen therapy less frequently, with a lower oxygen flow, and for a shorter duration; they received steroid therapy less often; they were less frequently admitted to ICU; and they less often needed high-flow oxygen or mechanical ventilation. Vaccinated patients 28-day survival was not statistically different, even though they presented more comorbidities.

The protective effect of vaccination was also observed when considering only older patients (>65 years), as illustrated in Fig. 1.

### Factors associated with severity

In bivariate analysis, vaccination and a previous SARS-CoV-2 infection were protective toward ICU and oxygen requirement, but not 28-day mortality. Comorbidities, older age, male gender and a longer time lapse since the most recent vaccine injection (among vaccinated patients) were significantly associated with a negative outcome (Table 3). In addition, being hospitalised for Covid-19, and having an elevated CRP, a low Cycle threshold and extensive lung lesions on CT scanner were associated with a negative outcome (Supplementary Table 1). When restricting these analyses to the patients who were hospitalised because of their Covid-19, the same associations were observed (suppl. Table 2).

Multivariate analysis confirmed the protective effect of vaccination regarding the need for oxygen, the need for ICU admission, and the risk of death. Vaccination was even able to offset the impact

**Table 2**  
Characteristics of patients with SARS-CoV-2 infection according to vaccinal status: Management and outcomes during hospital stay

	Vaccinated (N = 474)	Unvaccinated (N = 481)	p-value
Requirement for oxygen n (%)	229 (57.54) (N=398)	270 (72.97) (N=370)	<0.001
Maximal oxygen therapy (L/min)*	3.00 [0.00-8.75] (N=330)	6.00 [2.00-50.00] (N=320)	<0.001
Duration of oxygen therapy (days)*	3.00 [0.00-8.00] (N=304)	6.00 [2.00-12.00] (N=312)	<0.001
High-flow oxygen n (%)	49 (13.57) (N=361)	105 (29.41) (N=357)	<0.001
Steroid therapy			
prescribed n (%)	174 (47.15) (N=369)	250 (68.49) (N=365)	<0.001
dose median (IQR)	6.00 [6.00-7.50] (N=167)	6.00 [6.00-9.00] (N=238)	0.110
duration (days)	9.00 [5.00-10.00] (N=167)	10.00 [7.00-10.00] (N=240)	0.007
Tocilizumab n (%)	21 (6.31) (N=333)	59 (18.27) (N=323)	<0.001
Monoclonal Ab n (%)	27 (7.26) (N=372)	7 (1.93) (N=362)	<0.001
ICU admission n (%)	60 (16.22) (N=370)	133 (36.04) (N=369)	<0.001
Invasive mechanical ventilation n (%)	25 (6.91) (N=362)	59 (16.53) (N=357)	<0.001
Death at day 28 n (%)	74 (16.70) (N=443)	53 (12.24) (N=433)	0.075

Quantitative variables, identified with \* are presented as median (1<sup>st</sup> quartile - 3rd quartile). When data were missing the number of patients out of which the percentage was calculated is mentioned alongside the percentage.

of many risk factors such as hypertension and overweight (Table 4 and Supplementary Table 3); in addition to factors with odds ratio not statistically different from 1 presented in Table 4, many risk factors were finally not kept in the final multivariate model due to their negligible impact.

Moreover, in the multivariate regression model for death at day 28, the absence of significant interactions also showed that the protective effect of vaccination occurs for all patients, including those most at risk for severe forms such as older or immunosuppressed patients. In the multivariate regression model for oxygen requirement, an interaction between vaccination and a previous infection by Covid-19 was observed; the large coefficient associated with having previous Covid-19 infection suggests that it takes away most of the protective effect on oxygen requirement, leaving a small but still significant influence to vaccination.

## Discussion

The emergence of SARS-CoV-2 Delta VOC jeopardised the resolution of the Covid-19 pandemic; it was anticipated as being

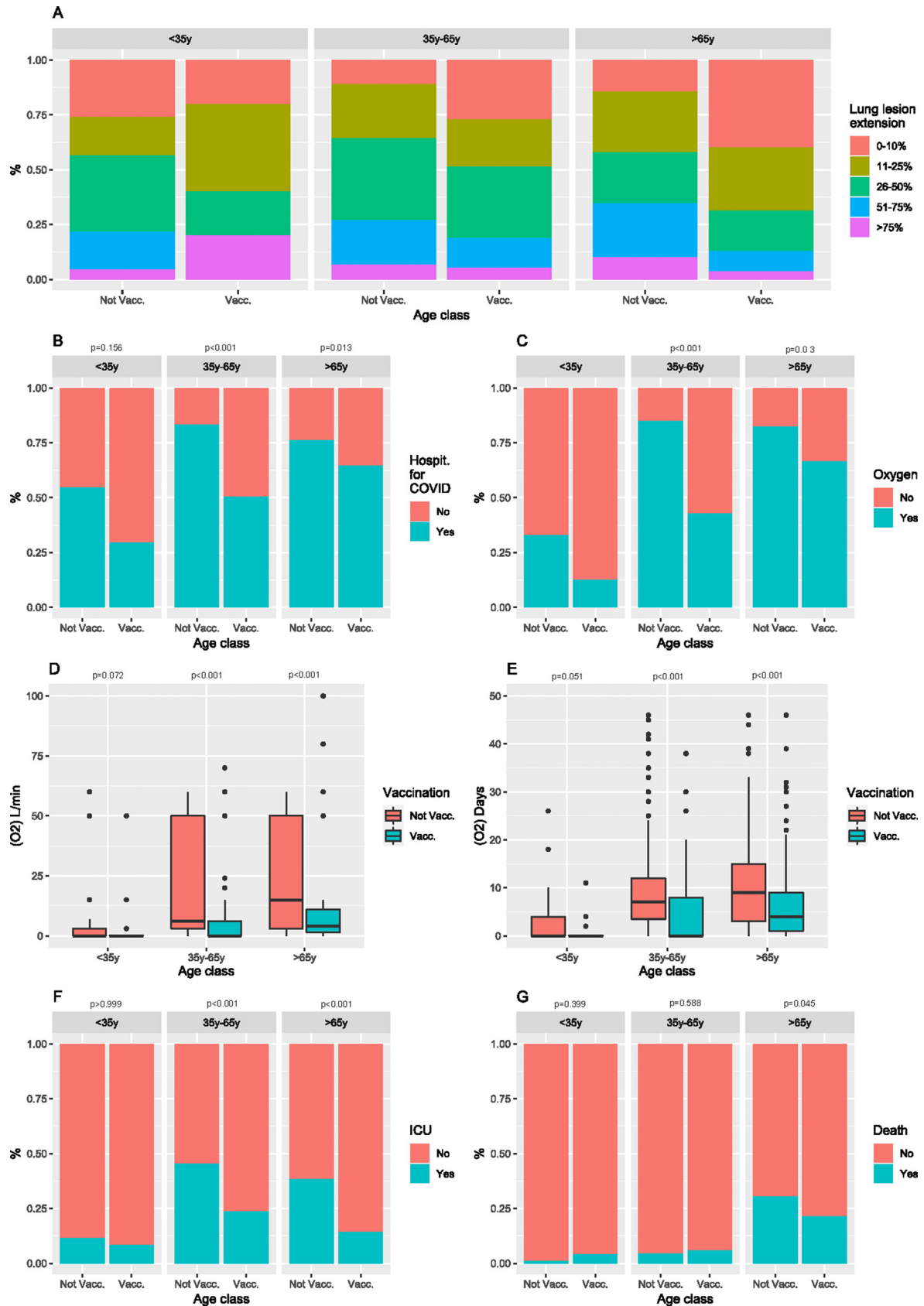
associated with breakthrough infections, as *in vitro* experiments showed that the neutralisation index of plasma from vaccinated individuals was lower for delta than for initial viral strain [9]. We therefore aimed to characterise the protection associated with vaccination towards the consequences of Delta VOC infection by studying the population of patients hospitalised with this infection. Including both patients hospitalised because of Covid-19 and those with incidental positive PCR while being admitted for another purpose allowed us to compare vaccinated and non-vaccinated patients not only with Covid-19 (i.e., symptomatic infection), but all infected patients: indeed, having an only asymptomatic form could result from the protection induced by vaccination.

We observed that vaccination retained and efficacy against Delta VOC infection: people hospitalised with a SARS-CoV-2 infection (whether for Covid-19 symptoms or for an unrelated cause) and vaccinated were less frequently admitted for Covid-19 symptoms, had less frequently hypoxia and lesser oxygen needs, and were less frequently admitted to ICU; in multivariate analysis, this reduction of severity persisted independently of age and comorbidities.

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

Factors	Death at day 28		ICU		Oxygen required	
	OR (IC95%)	p value	OR (IC95%)	p value	OR (IC95%)	p value
Age *	1.06 [1.05-1.08]	<0.001	0.99 [0.98-1.00]	0.049	1.02 [1.02-1.03]	<0.001
<35y	Ref.		Ref.		Ref.	
35-65y	2.93 (0.81-18.80)	0.157	5.17 (2.74-10.65)	<0.001	5.97 (3.66-9.9)	<0.001
>65y	17.91 (5.56-109.62)	<0.001	2.32 (1.23-4.77)	0.014	6.28 (3.92-10.29)	<0.001
Gender: Male	1.61 (1.10-2.38)	0.015	1.56 (1.12-2.19)	0.009	1.48 (1.10-2.00)	0.010
Diabetes mellitus	1.05 (0.67-1.61)	0.833	1.04 (0.71-1.52)	0.822	1.37 (0.97-1.97)	0.079
Hypertension	3.32 (2.23-5.01)	<0.001	1.00 (0.71-1.39)	0.978	1.68 (1.24-2.30)	<0.001
Tobacco, active or discontinued <3 years	0.48 (0.20-1.01)	0.077	0.87 (0.49-1.46)	0.602	0.49 (0.31-0.78)	0.002
BMI (kg/m <sup>2</sup> )	1.00 (0.96-1.03)	0.817	1.06 (1.03-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
Overweight (BMI>25 kg/m <sup>2</sup> )	1.17 (0.74-1.87)	0.514	3.30 (2.18-5.10)	<0.001	2.13 (1.53-2.99)	<0.001
Kidney failure (GFR<30)	4.55 (2.56-7.98)	<0.001	0.28 (0.10-0.61)	0.004	1.02 (0.58-1.84)	0.954
Respiratory disease	1.23 (0.75-1.96)	0.386	0.94 (0.60-1.44)	0.794	1.57 (1.05-2.40)	0.031
Oxygen at home	2.68 (0.92-6.94)	0.051	0.46 (0.07-1.67)	0.305	1.96 (0.68-7.01)	0.244
Cardiac failure	3.45 (2.04-5.77)	<0.001	0.68 (0.36-1.23)	0.224	2.11 (1.22-3.80)	0.010
Solid cancer (under treatment or for less than 3 months)	4.03 (1.71-9.13)	<0.001	0.44 (0.10-1.29)	0.183	0.58 (0.25-1.31)	0.184
Hematologic malignancy	2.39 (1.02-5.19)	0.034	0.78 (0.28-1.82)	0.588	0.71 (0.34-1.49)	0.353
Immunosuppression	2.23 (1.32-3.68)	0.002	0.91 (0.54-1.50)	0.723	1.00 (0.64-1.57)	0.986
At least one comorbidity	4.43 (1.80-14.73)	0.004	2.25 (1.26-4.35)	0.010	2.75 (1.74-4.38)	<0.001
Previous SARS-CoV-2 infection	0.17 (0.02-1.28)	0.086	0.10 (0.01-0.70)	0.021	0.13 (0.05-0.32)	<0.001
Time from last infection (days)	1.03 (0.95-1.11)	0.525	1.00 (0.99-1.01)	0.835	1.00 (0.99-1.00)	0.436
Vaccination	1.44 (0.98-2.11)	0.062	0.34 (0.24-0.48)	<0.001	0.50 (0.37-0.68)	<0.001
Time from last vaccine injection (days)	1.01 (1.00-1.01)	<0.001	1.00 (0.99-1.00)	0.341	1.01 (1.00-1.01)	<0.001

\* Results were comparable for age as a categorical variable. For death at day 28, and age <35y a the reference level, Age of 35-65y was not significantly associated with an OR: 2.93 (0.81-18.80) (p = 0.157) while age>65y was significantly associated with an OR: 17.91 (5.56-109.62) (p=<0.001). For ICU need, both age categories were significantly associated: 35-65y: OR = 5.17 (2.74-10.65) (p < 0.001) and >65y: OR = 2.32 (1.23-4.77) (p = 0.014). For oxygen requirement, both age categories were significantly associated: 35-65y: OR = 5.97 (3.66-9.9) (p < 0.001) and >65y: OR = 6.28 (3.92-10.29) (p < 0.001).



**Fig. 1.** SARS-CoV-2 infection severity criteria according to vaccine status in the three age classes. A: Extension of lung lesions on CT scanner; B: hospitalisation cause; C: Proportion of patients requiring oxygen; D: Maximal oxygen flow; E: Duration of oxygen therapy; F: Proportion of patients requiring ICU and G: Proportion of death at day 28.

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

Death on day 28	Best model	p-value	ICU admission	Best model	p-value	Need for oxygen	Best model	p-value
Vaccination	0.38 (0.20-0.70)	0.002	Vaccination	0.31 (0.21-0.47)	<0.001	Vaccination	0.16 (0.10-0.26)	<0.001
Male	2.65 (1.50-4.83)	0.001	Male	1.47 (0.99-2.21)	0.061	Male	1.66 (1.14-2.43)	0.008
Age	1.07 (1.04-1.10)	<0.001				Age	1.05 (1.03-1.06)	<0.001
Hypertension	1.64 (0.90-3.01)	0.107						
Overweight	1.75 (1.97-3.22)	0.066	Overweight	2.76 (1.77-4.38)	<0.001	Overweight	2.11 (1.44-3.11)	<0.001
Kidney failure (GFR<30)	2.71 (1.23-5.92)	0.013	Kidney failure (GFR<30)	0.41 (0.12-1.08)	0.102			
Immunosuppression	2.55 (1.22-5.23)	0.011						
Previous SARS-CoV-2 infection	0.27 (0.01-1.42)	0.212	Previous SARS-CoV-2 infection	0.11 (0.01-0.53)	0.031	Previous SARS-CoV-2 infection	0.01 (0.00-0.08)	<0.001
Solid cancer <3 months	5.04 (1.60-16.05)	0.005				Interaction term Vaccination x previous SARS-CoV-2 infection*	30.11 (3.26-90.16)	0.007

All the risk factors described in [Table 2](#) were included, after which variables with insignificant effect were retrieved. Namely, these variables with insignificant effect were:

- For "Death on day 28": Diabetes mellitus, tobacco, respiratory diseases, oxygen at home, cardiac failure, hematologic malignancy, at least one comorbidity, time from last infection.

- For "ICU admission": Age, Diabetes mellitus, hypertension, tobacco, respiratory diseases, oxygen at home, cardiac failure, Solid cancer <3 months, hematologic malignancy, immunosuppression, at least one comorbidity, time from last infection.

- For "Need of oxygen": Diabetes mellitus, tobacco, kidney failure, respiratory diseases, oxygen at home, cardiac failure, hematologic malignancy, immunosuppression, at least one comorbidity, time from last infection.

\* Taking into account this interaction, the odds ratio for oxygen requirement of a vaccinated patient without a previous COVID-19 would be 0.025 whereas it would be 0.010 with a previous COVID-19 infection.

Different studies and a meta-analysis assessing the impact of primary vaccination observed a  $\approx 10\%$  reduction in vaccine efficacy against asymptomatic and symptomatic infections with delta VOC, but no reduction of vaccine efficacy against severe forms [2], and 86-88% vaccine-associated reduction in the hospital admission rate in those infected with the delta VOC [10,11]. Our observations confirm the positive impact of vaccination on the severity of the SARS-CoV-2 delta infection, even in hospitalised patients. Moreover, we observed that the positive impact was maintained in populations at risk of severe Covid-19: those aged over 65 years, and those with pre-existing cardiac failure, kidney failure, or a chronic respiratory disease (at least for one or several severity criteria). All in all, this legitimates the prioritisation of these populations during the early months of the 2021 vaccine campaign: they benefited from valuable protection, even with the delta variant. Taken with previous fatality studies of vaccinated patients [11-13], this also confirms the perception shared by many physicians that vaccinated at-risk people presented in 2021 a milder form of Covid-19, while they might have not survived the more severe forms that are more frequent in those unvaccinated. Taking into account that overweight was more frequent among unvaccinated patients, while vaccination nonetheless effectively protected the associated mortality, emphasis should be made on this risk factor for severe forms of Covid-19.

The association between vaccination and less severe SARS-CoV-2 infection was less clearly evidenced in immunocompromised patients. The absence of interaction between vaccination and immunosuppression and the absence of a significant effect of immunosuppression in the model applied specifically to vaccinated patients suggest that vaccination is also efficient in immunocompromised patients (suppl. [Table 3](#)). Nonetheless, these results should not be over-interpreted as most of the immunocompromised patients in our cohort were vaccinated, and there is probably a lack of power to detect an interaction between both variables, or in other words a diminished effect of vaccination in immunocompromised patients. Moreover, immunocompromised patients remained at high risk of a severe form (OR = 2.55) even after adjustment for parameters such as other risk factors and vaccination ([Table 1](#)). Decreased efficacy in this population was

previously noted for virtually all vaccines, and was also observed with Covid-19 vaccines [14]. This led some countries (including France) to recommend an additional dose of the vaccine to these patients, and the prophylactic use of passive immunisation by monoclonal antibodies in immunocompromised patients with no or insufficient antibody response to vaccines [15].

As older patients were not only at risk of severe forms, but were also vaccinated earlier in the vaccination campaign, a lack of protection may have existed due to a waning of neutralising antibody titres over time after vaccination, an hypothesis previously proposed [16]. The multivariate analysis we specifically applied to vaccinated patients showed that both age and time from vaccination were associated with a significant increase in 28-day mortality. Once again, this confirms the need for a booster vaccine injection, particularly in those most at risk.

Our study has several limitations. Firstly, due to its retrospective design, some data retrieved from the medical files may have been erroneous or not completely accurate. However, the high number of studied patients, and comprehensive analysis on patients of known risk factors for adverse outcomes helped to reduce risk of biases. Secondly, we did not measure anti-Spike antibody titres in vaccinated patients at admission, a previously described predictive risk factor for SARS-CoV-2 infection and Covid-19 [17,18]; it would have helped to better understand whether severe infections in vaccinated subjects were due to waning of the neutralising antibody vaccine response. Although not significant, there was a trend among more death among vaccinated patients, which was offset during the multivariate analysis. While this may appear paradoxical, it simply illustrates the fact that vaccination is a proxy for at-risk patients, as they were prioritized during the vaccination campaign. Therefore, that vaccination is able to offset, completely or in part, the impact of comorbidities confirms its usefulness.

The implication suggested by these results is that even if escape from the vaccine-induced immune response is observed with SARS-CoV-2 VOC, vaccination with the original strain may still be associated with major protection. Those not yet vaccinated should be actively offered vaccination, even if *in vitro* studies show a partial decrease in vaccine-induced antibody neutralising activity; and

those already vaccinated should receive a booster, after a delay that may differ according to the properties of the VOC.

A new VOC, Omicron (B.1.1.529), has been responsible for a steep increase in SARS-CoV-2 infection in many countries since December 2022, and has replaced Delta as the predominant (or exclusively circulating) variant. Studies has shown that vaccine-induced antibodies had even lower neutralisation capacities toward Omicron, although the titres obtained after a booster injection are likely to retain protection [19]; vaccination is still associated with less severe forms in the first studies available [20]. A study similar to the present work would be relevant to better understand the impact of vaccination on this VOC. However, considering these first results on vaccine efficacy on the risk of Omicron severe infection, it is likely that the vaccine-induced protection we observed among hospitalised patients with a Delta infection is also present among those with an Omicron infection; the highest vaccine coverage should be reached even if new VOC emerge.

In conclusion, patients hospitalised with a SARS-CoV-2 infection with the Delta VOC have less marked severity criteria when they are vaccinated more than 14 days before hospitalisation, especially in case of elderly patients. These data should be provided when communicating information about Covid-19 vaccination with subjects at risk of severe Covid-19 because of their age or comorbidities.

#### Transparency declaration

None of the authors have any conflict of interest to disclose.

#### Funding

No external funding was received.

#### Authors' contributions

Conceptualization: OE, GB GC.

Methodology: OE, GB.

Software: OE, GB.

Validation: SA, ML, JFF, JM, EF, SB, CJ, AM.

Formal Analysis: OE, GB.

Investigation: OE, SA, ML, JFF, JM, EF, SB, CJ, AM, GB, GC, AF, SL, LS, PC.

Resources: not applicable.

Data curation: OE, GB, SA, ML, JFF, JM, EF, SB, CJ, AM.

Writing – Original Draft: OE, GB.

Writing – Review & Editing: SA, ML, JFF, JM, EF, SB, CJ, AM.

Visualization: OE, GB.

Supervision: OE, GB.

Administration: OE, GB.

Funding acquisition: not applicable.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2022.06.019>.

#### References

- [1] Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity after the BNT162b2 vaccine in Israel. *N Engl J Med* 2021;385:e85.
- [2] Harder T, Kulper-Schiek W, Reda S, Treskova-Schwarzbach M, Koch J, Vygen-Bonnet S, et al. Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection with the Delta (B.1.617.2) variant: second interim results of a living systematic review and meta-analysis, 1 January to 25 August 2021. *Euro Surveill* 2021;26.
- [3] Keehner J, Horton LE, Binkin NJ, Laurent LC, Pride D, Longhurst CA, et al. Resurgence of SARS-CoV-2 infection in a highly vaccinated health system workforce. *N Engl J Med* 2021;385:1330–2.
- [4] Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2-breakthrough infections to time-from-vaccine. *Nat Commun* 2021;12:6379.
- [5] Grannis SJ, Rowley EA, Ong TC, Stenehjem E, Klein NP, DeSilva MB, et al. Interim estimates of COVID-19 vaccine effectiveness against COVID-19-associated emergency department or urgent care clinic encounters and hospitalizations among adults during SARS-CoV-2 B.1.617.2 (delta) variant predominance – nine states, June–August 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1291–3.
- [6] Direction-de-la-recherche-des-études-de-l'évaluation-et-des-statistiques. Nine times more admission in critical care among unvaccinated persons compared with vaccinated persons in the population over 20 years] [Ministère de la Santé et des Solidarités; 2021. <https://drees.solidarites-sante.gouv.fr/communiquede-presseneuf-fois-plus-dentrees-en-soins-critiques-parmi-les-personnes-non-vaccinees>.
- [7] Akaike H, editor Information theory and an extension of the maximum likelihood principle. 2nd international Symposium on information theory 1971; Tsahkadzor, Armenia: Akadémiai Kiadó
- [8] Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol* 2017;17:162.
- [9] Davis C, Logan N, Tyson G, Orton R, Harvey WT, Perkins JS, et al. Reduced neutralisation of the Delta (B.1.617.2) SARS-CoV-2 variant of concern following vaccination. *PLoS Pathog* 2021;17:e1010022.
- [10] Poukka E, Baum U, Palmu AA, Lehtonen TO, Salo H, Nohynek H, et al. Cohort study of Covid-19 vaccine effectiveness among healthcare workers in Finland. *Vaccine* 2020;40:701–5.
- [11] Katikireddi SV, Cerqueira-Silva T, Vasileiou E, Robertson C, Amele S, Pan J, et al. Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil. *Lancet* 2022;399:25–35.
- [12] Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. *Nat Med* 2021;27:2136–43.
- [13] Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162b2 vaccine booster and mortality due to covid-19. *N Engl J Med* 2021;385:2413–20.
- [14] Marra AR, Kobayashi T, Suzuki H, Alsuhaibani M, Tofaneto BM, Bariani LM, et al. Short-term effectiveness of COVID-19 vaccines in immunocompromised patients: a systematic literature review and meta-analysis. *J Infect* 2022.
- [15] Ronapreve European\_Medicine\_Agency. (casirivimab and imdevimab) an overview of Ronapreve and why it is authorised in the EU. [https://www.euro.ema.europa.eu/documents/overview/ronapreve-epar-medicine-overview\\_en.pdf](https://www.euro.ema.europa.eu/documents/overview/ronapreve-epar-medicine-overview_en.pdf). 2021.
- [16] Bosch W, Cowart JB, Bhakta S, Carter RE, Wadei HM, Shah SZ, et al. COVID-19 vaccine-breakthrough infections requiring hospitalization in Mayo Clinic Florida through August 2021. *Clin Infect Dis* 2021.
- [17] Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021;27:1205–11.
- [18] Pierobon A, Zotto AD, Antico A, De Antoni ME, Vianello L, Gennari M, et al. Outbreak of SARS-CoV-2 B.1.617.2 (delta) variant in a nursing home 28 weeks after two doses of mRNA anti-COVID-19 vaccines: evidence of a waning immunity. *Clin Microbiol Infect* 2021.
- [19] Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature* 2022;602:671–5.
- [20] Kahn F, Bonander C, Moghaddassi M, Rasmussen M, Malmqvist U, Inghammar M, et al. Risk of severe COVID-19 from the Delta and Omicron variants in relation to vaccination status, sex, age and comorbidities - surveillance results from southern Sweden, July 2021 to January 2022. *Euro Surveill* 2022;27.