Serious hospital events following symptomatic infection with Sars-CoV-2 Omicron and Delta variants: an exposed-unexposed cohort study in December 2021 from the COVID-19 surveillance databases in France

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Abstract

Background: A rapid increase in incidence of the SARS-CoV-2 Omicron variant in France in December 2021, while the Delta variant was prevailing since July 2021.

Aim: To determine whether the risk of occurrence of a serious hospital event in adults following symptomatic SARS-CoV-2 infection differs for Omicron versus Delta.

Methods: A retrospective cohort study from 06/12/2021 to 07/01/2022. The outcome was a serious hospital event (admission to intensive care unit OR admission to critical care unit OR death). Omicron and Delta symptomatic cases were matched on the week of virological diagnosis and on age. Risk was adjusted for age, sex, vaccination status, presence of comorbidity and region of residence using Cox proportional-hazards model.

Results: 149,064 cases were included of which 497 had a serious hospital event (447 in the Delta arm, 50 in the Omicron arm). The risk of serious event was lower among Omicron versus Delta cases (adjusted Hazard Ratio, aHR=0.13 CI95 0.09-0.18 in 18 to 79 yo, aHR=0.30 CI95 0.17-0.54 in 80+ yo). The risk increased sharply with age and was lower in vaccinated compared to unvaccinated, without interaction between variant and vaccination status (aHR=0.15 CI95 0.11-0.19 for 18-79 yo with primary vaccination versus unvaccinated), was higher in cases with comorbidities (aHR = 3.70 CI95 2.66-5.13 for 18-79 yo with very-high-risk comorbidity versus no comorbidity) and in males.

Conclusion: This study confirms the lower severity of Omicron. The vaccine protection is essential in the elderly as they have a high risk of severe hospital events following infection with Omicron, even if much this risk is lower than with Delta.

Introduction

The Omicron variant (B.1.1.529, BA.*) of SARS-CoV-2 was first reported on November 23 2021, in Gauteng Province, South Africa [1]. The World Health Organization (WHO) designed Omicron variant of concern (VOC) due to more than 30 changes to the spike protein of the virus, its greater transmissibility, an increased risk of reinfection and its potential immune escape. As in many other European countries, sequencing data have shown a rapid increase in the Omicron variant in France: it represented 10.7% of interpretable sequences on 13 December 2021, almost 50% of those on 20 December 2021 and 89% during the first week of 2022. As of January 3, 2022, the Omicron variant has been detected in all regions of mainland France and overseas territories [2, 3]. Substantial decreases in severity of Omicron cases in comparison with Delta cases has been considered in different studies. First descriptive analyses conducted in South Africa compared the Omicron-dominant wave to previous SARS-CoV-2 waves. They observed fewer hospitalizations, less severe cases (including less admission to intensive care, less patient requiring oxygen therapy and lower
death rate) and a shorter length of hospital stay (3 days versus 7-8 days) during the Omicron wave [4-8]. However, the decrease in disease severity among Omicron cases could reflect changes in the characteristics of the infected population. Descriptive analyses comparing distinct epidemic waves do not allow concluding with certainty on a lower severity of the Omicron cases compared to Delta cases. An analytical approach allowing to reduce confounding factors as much as possible is necessary to conclude. The main objective of this study was to determine whether the risk of occurrence of a serious hospital event in adults following symptomatic SARS-CoV-2 differs for Omicron versus Delta, taking into account the main factors associated with the occurrence of a serious hospital event.

**Methods**

**Study design**

This is a retrospective cohort study carried out by combining the French COVID-19 surveillance databases. The study covers the period from 06/12/2021 to 07/01/2022. During this period, the variants Omicron and Delta circulated in France. The outcome of the study was the occurrence of a serious hospital event associated with COVID-19 (admission to intensive care unit OR admission to critical care unit OR death), among symptomatic persons testing positive for SARS-CoV-2, classified as Delta or Omicron using mutation screening. The cohort had two arms, consisting of Delta and Omicron variant cases respectively. Individual matching was performed on the calendar week of virological diagnosis, to compare contemporary cases, and on age, which is a major risk factor for the occurrence of severe events. In addition to matching, adjustment for four known risk factors (age, sex, vaccination status and presence of comorbidity) and region of residence was performed using Cox proportional-hazards model.

**Data sources**

To carry out its surveillance missions, Santé publique France receives pseudonymised health data from three information systems placed under the responsibility of the Ministry of Health. These three databases respectively include results of all SARS-CoV-2 tests (RT-PCR and antigen tests, excluding self-tests) performed in the country (SI-DEP), summary data on hospital stays, outcomes and types of wards (SI-VIC) and COVID-19 vaccine status and comorbidities of the whole French population» (VAC-SI). The extraction of data for events that took place from 06/12/2021 was carried out on 11/01/2022. As four days are required for 90% of hospital events to be reported in the SI-VIC database, events after 07/01/2022 were excluded to control for reporting bias. A pseudonym, based on the surname, first name, date of birth, sex of the patients and a hash key was used to merge the three data sources.

**Eligibility criteria**

Persons older than 18 years on the day of inclusion, sampled for SARS-CoV-2 diagnostic between 06/12/2021 and 02/01/2022 (inclusive) and declared as symptomatic at sampling, with a confirmed SARS-CoV-2 infection and valid RT-PCR mutation screening were included. Exposed persons are those with a strong suspicion of the Omicron variant (see below). Non-exposed persons are those with a strong suspicion of the Delta variant, based on the screening results. Persons with missing data, as well as those not found in the VAC-SI database or with an inconsistent vaccination status were excluded.

**Variables**

**Virological analysis**

For persons with several positive RT-PCR tests with valid mutation screening results over the period, the first one was selected. For each case, it was investigated whether another positive test without mutation screening result (RT-PCR or antigen test) had been performed in the 15 days preceding the date of sampling of the RT-PCR test with screening. If this was the case, the date of inclusion in the cohort was the date of sampling for this test.
Variant
In France, a proportion of the samples that tested positive for SARS-CoV-2 by RT-qPCR are further characterized using a mutation screening multiplex RT-qPCR targeting a set of predefined mutations (supplementary material). Target mutations included in this mutation screening strategy are defined at a national level according to their impact on the characteristics of the SARS-CoV-2 and their frequency in circulating variants. Over the study period, mutation screening results were submitted to the national SARS-CoV-2 test database SI-DEP in three variables: A for the detection of Spike mutation E48K, C for the detection of Spike mutation L452R, and D for the detection of one among several Spike mutations associated with Omicron (deletion 69-70 or substitutions K417N, N501Y, S371L-S373P or Q493R). An algorithm was designed to determine the most likely variant (Delta, Omicron, Other/Inconclusive) from the mutation screening profiles. The detection of L452R (coded C1 in SI-DEP) was used as a proxy for the Delta variant. The absence of both E484K and L452R (coded A0C0) or the detection of one of the mutations associated with Omicron (D1) was used as a proxy for the Omicron variant. To validate this algorithm, a study was performed on 11,574 results with sampling between 01/12/2021 and 10/01/2022 for which a mutation screening result and an interpretable sequencing result were available. The variant assigned by the algorithm was compared with the one identified by sequencing. The specificity of classification using mutation screening data was estimated to be 99.1% for Delta and 92.9% for Omicron. The detailed results of this validation are given in the supplementary material.

Vaccination status
Vaccination status at inclusion was determined by taking into account injections received. For each person it was determined whether, at the date of inclusion, he or she was unvaccinated, vaccinated with a complete primary vaccination or vaccinated with a primary vaccination and a booster. The vaccination status is recorded in real time by the vaccinator and takes into account the number of injections recommended in certain situations such as a history of infection or immunosuppression; these situations may lead to the injection of one more or less dose. Injections given less than 14 days before the date of inclusion in the cohort, for the first, and less than 7 days for the others were not retained. Persons with an incomplete primary vaccination schedule were considered unvaccinated.

Comorbidities
The presence of comorbidities inducing a very high risk of complication is an item of VAC-SI. The comorbidities were classified by distinguishing between patients with a very-high-risk and medium-risk comorbidity. Very-high-risk comorbidities included cancers, haematological malignancies undergoing chemotherapy, severe chronic kidney disease, chronic dialysis, solid organ transplants, haematopoietic stem cell allografts, chronic multi-disease conditions with two or more organ failures, certain rare diseases and those at particular risk of infection (9), and Down's syndrome (10). Medium-risk comorbidities included: obesity, diabetes, chronic renal failure, COPD and respiratory failure, hypertension, heart failure.

Hospital events
Only patients hospitalised “for Covid” (as opposed to “with Covid”, i.e. tested positive for SARS-CoV-2 but hospitalised for a reason other than COVID-19) were included in the study. A person was considered to have had a “serious hospital event”, if he or she was admitted to an intensive care unit (ICU) or critical care unit (CCU) or died in hospital during the study period. Two or three of these events may be observed for the same person. The date of occurrence of the serious hospital event was then the earliest of these. People tested at the hospital on the day of hospitalisation were included in the study.

Matching
Each exposed person (infected with Omicron) was individually matched with an unexposed person (infected with Delta) of the same age range (18-39, 40-64, 65-79, 80+) and with an inclusion date in the same calendar week. Unmatched individuals were excluded.
Statistical methods

Descriptive analyses were conducted for all variables. The chi-square test was used to compare the distributions of the event of interest and the evolution of the cohort size over the follow-up period. Descriptive analyses were stratified according to the two variants. Univariate and multivariate analyses were performed using Cox proportional-hazards model, proportional hazard survival models. Individual matching was taken into account in models. The multivariate models include the variables selected from the univariate analyses (p <0.2). Interactions were tested between variants and age, sex, vaccination status and comorbidities. The final multivariate model was constructed through a two-way stepwise selection process based on AIC. The analyses were performed using R. 4.0.4

Results

Participants

The numbers at different stages of the inclusion process are as follows:

- People over 18 with symptoms, sample taken during the inclusion period and RT-PCR positive with a valid result for mutation screening: 414,527
- Exclusion of 8,956 persons with missing sex or postal code in SIDEP: remaining 405,571
- Exclusion of 64,059 persons not found in VAC-SI: remaining 341,512
- Matching: 74,532 pairs constituted (149,064 persons) and exclusion of unmatched persons

Descriptive data

Numbers in the two arms of the cohort reflected the dynamic of the spread of the Omicron variant in France during December 2021 (Table 1). Few people were included during weeks 49 and 50 because the Omicron variant was then uncommon in France. The vast majority of inclusions took place during weeks 51 and 52. Geographically, the Île-de-France region accounted for 23% of those infected with the Omicron variant and only 6.7% of those infected with the Delta variant; this region has been indeed the first to be largely affected by the Omicron variant. Conversely, the Delta variant was still very frequent in the Provence-Alpes-Côte-D’Azur and Occitanie regions during the four weeks of the study. The gender distribution was very similar between the two arms, although the difference was statistically significant. The distribution of vaccination status was very different between the two arms of the cohort. The percentage of unvaccinated individuals was more than twice as high in the DELTA arm as in the OMICRON arm (36% vs. 17%). Overall, 84% of first injections were with Pfizer/BioNTech vaccine, 9.5% with Moderna, 5.0% with AstraZeneca and 1.2% with Janssen; there was no difference between the two arms. The distribution of comorbidities was statistically different between the two arms, with slightly more comorbidities in the DELTA arm, but this difference was small (Table 2). The percentage of people who have had a booster shot increased very strongly with age (Table 3). This reflects the phased roll-out of vaccination in France since the beginning of 2021.

Table 1. Distribution of included cases infected by the Omicron or Delta variant of the SARS-CoV-2 by calendar weeks of inclusion and region of residence, December 2021-January 2022, France, (n=149,064)

| Week       | DELTA     | OMICRON   | p-value |
|------------|-----------|-----------|---------|
| 2021-49    | 1,700 (2.3%) | 1,700 (2.3%) | >0.9    |
| 2021-50    | 8,387 (11%)  | 8,387 (11%)  |         |
| 2021-51    | 33,732 (45%) | 33,732 (45%) |         |
| 2021-52    | 30,713 (41%) | 30,713 (41%) |         |
| Region     |           |           | <0.001  |
| Grand Est  | 9,430 (13%)  | 6,773 (9.1%)  |         |
| Auvergne-Rhône-Alpes | 14,278 (19%) | 14,163 (19%) |         |
| île-de-France | 4,962 (6.7%) | 16,894 (23%) |         |
### Table 2. Distribution of included cases infected by the Omicron or Delta variant of the SARS-CoV-2 by sex, age, vaccination status and comorbidities, December 2021-January 2022, France, (n=149,064)

|               | DELTA       | OMICRON     | p-value |
|---------------|-------------|-------------|---------|
| Sex F         | 40,696 (55%)| 40,095 (54%)| 0.002   |
|               | 33,836 (45%)| 34,437 (46%)|         |
| Age [18,40)   | 41,679 (56%)| 41,679 (56%)| >0.9    |
|               | 28,097 (38%)| 28,097 (38%)|         |
| [65,80)       | 3,795 (5.1%)| 3,795 (5.1%)|         |
| [80,Inf)      | 961 (1.3%)  | 961 (1.3%)  |         |
| Vaccination   |             |             | <0.001  |
| Unvaccinated  | 25,466 (34%)| 11,972 (16%)|         |
| Primary vaccination | 44,280 (59%)| 50,470 (68%)|         |
| Booster       | 4,786 (6.4%)| 12,090 (16%)|         |
| Comorbidity   |             |             | <0.001  |
| None          | 63,392 (85%)| 64,783 (87%)|         |
| Medium-risk   | 9,018 (12%) | 7,951 (11%) |         |
| Very-high-risk| 2,122 (2.8%)| 1,798 (2.4%)|         |

### Table 3. Vaccination status by age group, December 2021, France, (n=149,064)

|               | [18,40) | [40,65) | [65,80) | [80,Inf) | p-value |
|---------------|---------|---------|---------|----------|---------|
| N             | 83,358  | 56,194  | 7,590   | 1,922    |         |
| Vaccination   |         |         |         |          | <0.001  |
| Unvaccinated  | 22,081 (26%)| 13,227 (24%)| 1,661 (22%)| 469 (24%)|         |
| Primary vaccination | 56,331 (68%)| 34,954 (62%)| 2,915 (38%)| 550 (29%)|         |
| Booster       | 4,946 (5.9%)| 8,013 (14%)| 3,014 (40%)| 903 (47%)|         |

### Follow-up and outcome data

The maximum follow-up time was 32 days, however, very few people were followed up over this period (Figure 1). This was expected, as few people were included in the first two weeks of the study. However, 81% of people were followed up for at least 10 days. A total of 497 serious hospital events were observed during the follow-up period (Table 4). The number of serious hospital events was significantly higher in the DELTA arm (447) than in the OMICRON arm (50). The most frequent event was admission to the intensive care unit. The sum of the numbers of ICU admissions, CCU admissions and deaths is higher than the number of serious events, as the same person may be involved in more than one type of event. In the DELTA arm of the cohort, 92% of serious events were observed within 14 days of positive sampling, and 97% within 21 days. In the OMICRON arm, 84% of events occurred within 14 days and 100% within 20 days (Figure 1).
Table 4. Observed hospital events during the follow-up period, December 2021-January 2022, France, (n=149,064)

| Event                      | DELTA   | OMICRON | p-value |
|---------------------------|---------|---------|---------|
| Serious hospital event    | 447 (0.6%) | 50 (<0.1%) | <0.001 |
| Intensive Care Unit admission | 259 (0.3%) | 20 (<0.1%) | <0.001 |
| Critical Care Unit admission | 148 (0.2%) | 17 (<0.1%) | <0.001 |
| Death                     | 116 (0.2%) | 19 (<0.1%) | <0.001 |

Figure 1. Evolution since the virological diagnosis of the cumulative probability of a serious hospital event among cases infected by the Omicron or Delta variant of the SARS-CoV-2, December 2021-January 2022, France, (n=149,064)
Univariate analysis

The crude hazard ratio for a serious hospital event was statistically different between the two arms of the cohort for all covariate modalities, except for the region (statistically significant for 4 of the 13 regions, Table 5). Table 6 gives the absolute number of serious events observed per 100,000 people within 21 days of positive sampling, for each covariate value. The number of serious events was greater for those with a booster than for those with a complete primary vaccination. This counter-intuitive observation is analysed in the multivariate model.

Table 5. Univariate analysis using Cox regression for the risk of a serious hospitalisation event among cases infected by the Omicron or Delta variant of the SARS-CoV-2, December 2021-January 2022, France (n= 149,064)

| Variant       | DELTA | OMICRON | cHR  | 95% CI         | p-value  |
|---------------|-------|---------|------|----------------|----------|
| **Age**       |       |         |      |                |          |
| [18,40)       | 0.14  | Ref     | 0.12 | [0.09 - 0.16]  | <0.001   |
| [40,65)       | 6.65  | Ref     | -    | [5.41 - 8.19]  | <0.001   |
| [65,80)       | 16.04 | Ref     | -    | [12.55 - 20.49]| <0.001   |
| [80,Inf)      |       |         |      |                |          |
| **Sex**       |       |         |      |                |          |
| F             | 1.84  | Ref     | -    | [1.53 - 2.2]   | <0.001   |
| M             |       |         |      |                |          |
| **Vaccination**|      |         |      |                |          |
| Unvaccinated  |       | Ref     | -    |                |          |
| Primary vaccination | 0.13 | [0.1 - 0.16] | <0.001 |
| Booster       | 0.33  | Ref     | -    | [0.24 - 0.46]  | <0.001   |
| **Comorbidity**|      |         |      |                |          |
| None          |       | Ref     | -    |                |          |
| Other         | 6.27  | [5.18 - 7.59] | <0.001 |
| Very High Risk| 10.02 | [7.65 - 13.12]| <0.001 |

*cHR = crude Hazard Ratio, CI = Confidence Interval

Table 6. Cumulative probability at D21 of a serious hospital event among cases infected by the Omicron or Delta variant of the SARS-CoV-2, stratified by co-variables, December 2021-January 2022, France, (n= 149,064)

|         | DELTA | OMICRON |
|---------|-------|---------|
| **Age** |       |         |
| [18,40) | 96    | [65 - 127] |
| [40,65) | 689   | [586 - 791] |
| [65,80) | 4,544 | [3784 - 5299] |
| [80,Inf)| 10,653| [8040 - 13191] |
| **Sex** |       |         |
| F       | 429   | [364 - 494] |
| M       | 816   | [718 - 915] |
| **Vaccination**|     |         |
| Unvaccinated | 1,226| [1090 - 1362] |
| Primary vaccination | 213 | [169 - 257] |
| Booster  | 654   | [410 - 898] |
| **Comorbidity**| |         |
| None    | 334   | [288 - 379] |
| Medium-risk | 1,991| [1688 - 2294] |
| Very-high-risk | 3,365| [2500 - 4222] |

Kaplan-Meier estimator and 95% CI
Multivariate analysis

As the univariate analysis showed that all the variables were related to the occurrence of a serious event (p<0.2), they were all included in the multivariate analyses. Models were adjusted for region of residence, but this variable is not presented in the tables for simplicity. The overall model (not shown) showed a risk reduction in the Omicron arm (adjusted Hazard Ratio = 0.10), but also an interaction between variant and age, which means that the hazard ratio between Delta and Omicron is not identical in all age groups. To simplify the interpretation of the results, two sub-models are presented: one for people aged 18-79 and the other for people aged 80 and over (Table 7). No interaction was found between age and vaccination in the 18-79 year old model. People aged 18-79 years with symptomatic infection by the Omicron variant had a 7.7 times lower risk (5.6-11.1) of having a serious hospital event than those with symptomatic infection by Delta [HR=0.13; CI95 0.09-0.18]. In people aged 80 years and over, the difference in risk between the two variants was smaller: Omicron cases had a 3.3-fold lower risk (5.6 to 11.1) than Delta cases [HR=0.30; CI95 0.17-0.54].

The risk of a serious event increased sharply with age: the absolute risk for the reference population (unvaccinated women without comorbidity, infected with Delta) was 140/100,000 for 18 year olds [95% CI 81-199], 913 [603-1,214] for 40-64 yo, 4,844 [2,999-6,427] for 64-79 yo, and 58,419 [6,160-66,872] for ≥ 80 yo. The models also highlighted the levels of risk associated with other covariates: the risk was almost twice as high for men as for women, with no major difference between those aged 18 to 79 and those aged 80 and over; the risk was reduced in vaccinated people. Between the ages of 18 and 79, the risk was divided by 6.7 for those who had been vaccinated, whether or not they had received a booster [HR=0.15]. In people over 80 years of age, the risk was divided by 4.3 with a booster and 2.2 with a primary vaccination [HR=0.23 and 0.46]; the risk was increased in case of co-morbidity in 18-79 year olds (3.7 times for very-high-risk comorbidity and 2.8 times for medium-risk comorbidities). In the over 80s the risk associated with comorbidities was not statistically significant.

Table 7. Multivariate analysis using Cox regression for the risk of a serious hospitalisation event among cases infected by the Omicron or Delta variant of the SARS-CoV-2, stratified by age, December 2021-January 2022, France (n= 149,064)

| Variant       | Age [18,80) | Age [80,Inf) |
|---------------|-------------|--------------|
|               | aHR¹        | 95% CI¹      | p-value | aHR¹        | 95% CI¹      | p-value |
| DELTA         | Ref         | -            | -       | -           | -            | -       |
| OMICRON       | 0.13        | 0.09 – 0.18  | <0.001  | 0.30        | 0.17 – 0.54  | <0.001  |
| Age           |             |              |         |             |              |         |
| [18,40)       | 0.15        | 0.11 – 0.21  | <0.001  | -           | -            | -       |
| [40,65)       | Ref         | -            | -       | -           | -            | -       |
| [65,80]       | 5.30        | 4.23 – 6.65  | <0.001  | -           | -            | -       |
| Sex           |             |              |         |             |              |         |
| F             | Ref         | -            | -       | -           | -            | -       |
| M             | 1.93        | 1.58 – 2.37  | <0.001  | 1.78        | 1.17 – 2.69  | 0.007   |
| Vaccination   |             |              |         |             |              |         |
| Unvaccinated  | Ref         | -            | -       | -           | -            | -       |
| Primary vaccination | 0.15   | 0.10 – 0.22  | <0.001  | 0.23        | 0.12 – 0.43  | <0.001  |
| Booster       | 0.15        | 0.10 – 0.19  | <0.001  | 0.46        | 0.28 – 0.74  | 0.002   |
| Comorbidity   |             |              |         |             |              |         |
| None          | Ref         | -            | -       | -           | -            | -       |
| Medium-risk   | 2.80        | 2.23 – 3.52  | <0.001  | 1.24        | 0.79 – 1.97  | 0.4     |
| Very-high-risk| 3.70        | 2.66 – 5.13  | <0.001  | 1.72        | 0.91 – 3.24  | 0.10    |

¹HR = adjusted Hazard Ratio, CI = Confidence Interval
**Discussion**

**Key results**

Our national cohort study confirms the lower severity of Omicron infections compared to Delta infections in adults, by quantifying the risk of a serious hospital event i.e. the admission in intensive care unit (ICU), critical care unit (CCU) or death during hospitalization. We defined this outcome as death may occur in patients not admitted to ICU wards, such as frail elderly patients. [9]. People aged 18 to 79 years had a 7.7 times lower risk of severe outcome when infected with the Omicron variant (HR=0.13). However the risk ratio was only of 3.3 in the 80 year-olds and older (HR=0.30).

Substantial decrease in severity of Omicron cases compared with Delta cases has been considered in different studies. In South Africa, after controlling for factors associated with hospitalization, individuals with S Gene Target Failure (SGTF), used as a proxy for Omicron infection, had lower odds of being admitted to hospital compared to non-SGTF infections, used as a proxy of Delta infection (0.2, 95%CI 0.1-0.3). However, the Delta and Omicron cohorts in this study were not contemporaneous and the Omicron cohort had more acquired immunity which might have lessened the estimated severity of Omicron. [10] Studies with contemporary cohorts have since been conducted in Canada [11], the USA [12], UK [13] and Norway [14]. Our results align with findings in Ontario, Canada; this matched cohort study described a reduction of 83% (HR: 0.17; CI95 0.08-0.37) in admission to intensive care unit or death for Omicron cases when compared to Delta cases. In the United States (California), the hazard ratios between Delta and Omicron cases, after a positive outpatient test, were 0.26 (CI95 0.10-0.73) for admission to intensive care and 0.09 (CI95 0.01-0.75) for death. In the UK, the reduction in the risk of hospitalisation during a 4-day follow-up was 65%. In Norway, Omicron was associated with an overall 73% reduced risk of hospitalisation (HR = 0.27 CI95 0.20–0.36) compared with Delta.

The study also quantified the protection provided by vaccination. In Norway, an interaction between the variant and vaccination status was detected in the subgroup of people with primary vaccination completed 7-179 days ago, suggesting a weaker effectiveness of the vaccine for Omicron cases than for Delta cases (66% and 93%, respectively) [14]. In our study we did not find evidence of such an interaction although the size of our cohort is larger; however, our study focused on severe hospital events whereas the Norwegian study considered all hospital admissions, suggesting that the effectiveness of vaccination against severe forms of COVID-19 is equivalent for both variants. Nevertheless, as the individuals were symptomatic at inclusion in the cohort, our results did not take into account either the possible differential capacity of the two variants to cause symptomatic infection, or the capacity of the vaccines to prevent symptomatic infection. The fact that we observed 44% of unvaccinated individuals in the Delta arm and only 20% in the Omicron arm seems to support a partial vaccine escape for the prevention of symptomatic infection by the Omicron variant as reported in other studies. Nevertheless, vaccination remained effective in preventing serious hospital events. Further studies are needed to better understand the differences between Delta and Omicron ahead of symptomatic infection. Buchan and al also showed that two doses of COVID-19 vaccines were unlikely to protect against infection by Omicron (irrespective of symptoms or severity) and vaccine effectiveness against this variant was only 37% (95%CI, 19-50%) ≥7 days after receiving an mRNA vaccine for the third dose in a population with a high proportion of immunosuppressed patients [15]. The duration of this protection and effectiveness against severe disease are uncertain. In contrast, after 2 doses of COVID-19 vaccine, vaccine effectiveness against Delta infection declined steadily over time but recovered to 93% (95%CI, 92-94%) ≥7 days after receiving an mRNA vaccine for the third dose [15].

The risk of ICU admission, CCU admission or death was almost three times higher for patients with comorbidities than for those without, with a tendency to be higher for “very high risk” comorbidities. The absence of interaction showed that this excess risk was present for both variants. The higher risk of developing severe COVID-19 infection in patients with underlying medical comorbidities has been widely described and may lead to up to a six-fold increase in hospitalisation [16].
The risk of ICU admission or death was almost two times higher among males compared to females. The absence of interaction evidenced in our study is in favour of this excess risk existing for both variants. The increased risk of developing severe COVID-19 infection and increased mortality due to COVID-19 for male has already been described [16-18].

Strengths of the study
Studies comparing consecutive waves of the epidemic may lead to confounding biases as the decrease in disease severity in the Omicron cohort could reflect an increase in the vaccination rate, a change in the characteristics of the infected population or a change in hospital care over time. In our study, to control such a bias, each Omicron case was matched on age and date of onset to a Delta case. In addition, a multivariate analysis was used to adjust the hazard ratio of severe events between Delta and Omicron variants infections on gender, age, vaccination status and comorbidities, which are known risk factors for severe forms of COVID-19. Cox proportional hazards models allowed for different follow-up times.

The time required to integrate 90% of the data into the SI-VIC database is estimated to be 4 days. This was taken into account by stopping the follow-up four days before the data extraction. The duration of follow-up was ≤ 33 days and 81% of cases were followed for at least 10 days. This duration was longer than in a United Kingdom cohort followed during the very first days of the Omicron wave [13]. This appears to be long enough, as 92% of serious events following symptomatic Delta infection and 84% following symptomatic Omicron infection occurred within 14 days of virological diagnosis. Infections diagnosed from the day after hospitalisation were not included, preventing the risk of nosocomial infections being included in the study.

All cases included in this study were screened by RT-PCR in order to identify a set of target mutations. We designed an algorithm to classify cases in suspected Delta cases, suspected Omicron cases and other variant/inconclusive. Using cases for which a sequencing result was also available, we found a specificity of our algorithm of 99.1% for Delta and 92.9% for Omicron. PCR screening did not allow to segregate between the two main Omicron sub-lineages, BA.1 and BA.2, but as of 15 January 2022, BA.2 was very rarely detected in France. It is also important to note that the algorithm used in this study was designed according to the variants circulating in France during the study period, and might not be adaptable to other timeframes

Limitations
In this study, vaccination status was characterised only by discriminating between the non-vaccinated, the primo-vaccinated and the booster-vaccinated. Studies with more power are needed to assess other parameters, such as the time between the last injection and exposure or the type of vaccine. According to a study, the injection of a booster dose reduces the risk of hospitalization of Omicron cases between 70 and 88% [19, 20] and severe forms by 98% [21]. Although, information on a known previous infection is used to determine the required number of injections (e.g. one single dose for primary vaccination in case of known previous infection), it was not possible to take into account this information in our model, but it would be useful to include it in future studies.

Another limitation is the imperfect merge, by pseudonym, between the three databases: 16% of the persons fulfilling the inclusion criteria in SI-DEP were excluded because they were not found in VAC-SI. It is also possible that not all hospital events were found in SI-VIC. However, there is no reason why this loss of information should differ between the two arms of the cohort and therefore affect the risk ratios.

Conclusion
This cohort study provides results to better understand the severity of the Omicron variant compared to the Delta variant. It confirms and quantifies the lower severity of Omicron, which has been suggested since the emergence of this variant. Even if vaccines have a lower efficacy against infection by the Omicron variant compared to the Delta variant, protection against severe events does not appear to differ between the two variants. The vaccine protection is all the more essential
in the elderly as they have a higher risk of severe hospital events following infection with Omicron than younger subjects, even if this risk is much lower than with Delta.

Authors’ contributions

SV, DLB, IPC, BC and YLS conceived and designed the study; SV reviewed the literature; JS and LF designed the algorithm for assigning a variant using PCR screening results which specificity was assessed by JS and VA; CM and VA managed the datasets. VA did the statistical analysis with the help of YLS and LF.; VA and SV wrote the original draft, and all authors reviewed and edited the manuscript.

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Statements

Conflict of interest statement

All authors have nothing to declare.

Access to data

While all data used in this analysis were pseudonymised, the individual-level nature of the data used risks individuals being identified, or being able to self-identify, if it is released publicly. Requests for access to the underlying source data should be directed to Santé publique France and will be granted in accordance with the GDPR and French Law.

Ethical statement

This study did not involve the human person. It was carried out by Santé Publique France using existing pseudonymised health data collected from the information systems set up by the Ministry of Health to manage the Covid 19 crisis. Access to and analysis of this pseudonymised health data by Santé Publique France was carried out to fulfil its public interest mission of monitoring the health of the French population, as part of the response to the health crisis. This processing of personal data was implemented in accordance with the legislative and regulatory prerogatives granted to Santé Publique France to access these data and in compliance with the provisions of the GDPR. In this context, the opinion of an ethics committee was not required.

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