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Short communication

Vaccine effectiveness against COVID-19 hospitalization in adults in France: A test negative case control study

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ABSTRACT

Background: Measuring vaccine effectiveness (VE) using real-life data is critical to confirm the effectiveness of licensed vaccine, which could strengthen vaccination adherence.
Methods: We measured VE against adult COVID-19 hospitalization in five hospitals in France using a test negative design. We compared the odds of vaccinated patients hospitalized with COVID-19 with the odds of vaccinated patients hospitalized for the same symptoms with a negative test.
Results: A total of 853 patients (463 cases and 390 controls) were included, with a total of 170 patients vaccinated (104 with one dose, 65 with two doses, and one with three doses). There were four cases of breakthrough infections, all in immunocompromised patients. The VE was 84.0% ($CI_{0.95}$ = [72.6; 90.6]) for one dose and 96.2% ($CI_{0.95}$ = [86.8; 98.9]) for two doses.
Conclusion: Our results confirm the high VE of COVID-19 vaccine in France to prevent hospitalizations due to the alpha variant.

1. Background

France started COVID-19 vaccination on December 27, 2020. Initially restricted to residents of nursing homes and healthcare workers (HCW), it was gradually extended to all adults on May 31, 2021. On July 26, 2021, more than 40 million French residents (almost 60% of the total population) had received at least one dose of one of the four European Medicine Agency (EMA)-approved COVID-19 vaccines: mRNA BNT162b2 (Comirnaty®, Pfizer-BioNTech), mRNA-1273 (Spikevax®, Moderna), ChAdOx1 nCoV-19 (Vaxzevria®, AstraZeneca-Oxford University), and Ad26.COV2-S (Janssen®, Janssen). Measuring vaccine effectiveness (VE) using real-life data is critical to confirm the effectiveness of licensed vaccine, in addition to pivotal clinical trials which could strengthen vaccination adherence, which was particularly low in France during the first months of 2021 [1]. The Inserm Fluvac study, conducted since 2013 in five French hospitals (Paris-Cochin, Paris-Bichat, Rennes, Montpellier, Lyon), has been evaluating the effectiveness of influenza vaccines against hospitalization among adults using a test negative design [2]. The Fluvac network and study design have been adapted to study COVID-19 VE, and the first results are presented here.

2. Study population

Between December 23, 2020 and June 15, 2021, 853 patients hospitalized for influenza-like illness – defined as the combination of at least one general symptom (fever, malaise, headache, myal-

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Table 1
Characteristics of study population (France, December 21, 2020 to June 26, 2021).

Parameters	Control (n = 390)	Case (n = 463)	P-value
Age (median, IQR)	77.0 [62.0; 85.0]	66.0 [53.5; 76.5]	< 0.001
Sex (female, %)	185 (47.4%)	196 (42.3%))	0.135
Body mass index (median, IQR)	25.4 [22.1; 29.7]	26.9 [24.2; 30.9]	< 0.001
With a professional activity	40 (10.3%)	136 (29.4%)	< 0.001
Comorbidities (n, %)	330 (84.8%)	315 (68.2%)	< 0.001
Chronic respiratory disease	131/389 (33.7%)	84/462 (18.2%)	
Chronic cardiac disease	170/390 (43.6%)	101/462 (21.9%)	
Cirrhosis	25/389 (6.4%)	18/462 (3.9%)	
Immunosuppression	10/389 (2.6%)	13/462 (2.8%)	
Diabetes	96/389 (24.7%)	107/462 (23.2%)	
Auto-immune disease	19/389 (4.9%)	8/462 (1.7%)	
Obesity	102/390 (26.2%)	149/463 (32.2%)	
Cancer	56/389 (14.4%)	51/462 (11.0%)	
Oxygen (n, %)	263/390 (67.4%)	404/463 (87.3%)	
Length of stay (median, IQR)	8 [4; 13]	10 [6; 16]	
Admitted in the ICU	44/390 (11.3%)	121/462 (26.1%)	< 0.001
Length of stay (median, IQR)	3 [2; 6]	6 [4; 11]	
Invasive mechanical ventilation (%)	4 (1%)	33 (7%)	
Death	22/398 (5.5%)	26/462 (5.6%)	

IQR, interquartile range; ICU, intensive care unit.

gia, or fatigue) and one respiratory symptom (cough, sore throat, shortness of breath, or tachypnoea) – were included (Table 1). Patients were prospectively screened by research staff, and detailed clinical data on comorbidities, vaccination status, and vital status were collected at baseline as well as data on hospital stay and vital status at 30 and 90 days. All patients were tested by PCR technique for SARS-CoV-2 infection within 7 days of symptoms onset, according to local technique guidelines. Patients with a positive SARS-CoV-2 PCR test were classified as "COVID-19 cases", while those with a negative PCR test were classified as "controls". Among the 853 patients included, there were 463 cases and 390 controls. All cases presented with symptoms compatible with SARS-CoV-2 infection. Overall, 308 of 463 cases (67%) were directly diagnosed with SARS-CoV-2 pneumonia at admission. The remaining 155 cases were included for influenza-like illness (n = 101, 65%), respiratory symptoms (n = 98, 63%), fatigue (n = 80, 52%), and myalgia (n = 25, 16%). Several controls (n = 42, 11%) presented with cardiac disease associated with respiratory symptoms. Among control patients, only 19 respiratory viruses other than SARS-CoV-2 were observed. Cases were younger (median, 66 years vs. 77), had a higher body mass index (26.9 kg/m^2 vs. 25.4), more often had a professional activity (29.4% vs. 10.3%), and had fewer comorbidities (68.0% vs. 84.6%). Oxygen therapy was required for 87.3% of cases and 67.4% of controls. Length of stay was 10 days for cases and 8 days for controls. Cases more frequently required intensive ICU admission (26.1% vs. 11.3%), with an average ICU length of stay of 6 days for cases and 3 days for controls; 7% of cases required invasive mechanical ventilation versus 1% of controls (Table 1). The in-hospital mortality rate was 5.5% in the case group and 5.6% in the control group.

3. Vaccinated population

A total of 170 patients received at least one dose of COVID-19 vaccine before symptom onset: 50 in the case group (46 received one dose and four two doses) and 120 in the control group (58 received one dose, 61 two doses, and one three doses). Most vaccinated patients (127/170, 74.7%) had received Comirnaty® (Pfizer vaccine), followed by Vaxzevria® (24/170, 14.1%). Among the four cases hospitalized for COVID-19 after two doses, there were one man admitted less than 7 days after the second dose and three patients more than 7 days after the second dose: two women aged 79 and 42 years with kidney transplants, and one man aged 72 years with multiple myeloma on third-line chemotherapy. All these patients did not require intensive care, and were alive at discharge and one month later (Table 2).

4. Vaccine effectiveness calculation

VE was estimated using a test negative design. We compared the odds of vaccinated patients hospitalized with COVID-19 with the

Table 2
Characteristics of vaccine breakthroughs.

Patient	Age	Sex	PCR results for SARS-CoV-2	Condition	Time from vaccination to symptoms (days)	Time from symptoms to hospitalization (days)	Length of stay (days)	Vital status at one month
1	75	M	+	Splenectomy Cirrhosis Multiple myeloma	3	6	25	Alive
2	79	F	+	Splenectomy Kidney transplant	14	4	23	Alive
3	42	F	+	Cardiac condition Kidney transplant Obesity	18	4	13	Alive
4	82	M	+	Multiple myeloma Renal failure	37	4	31	Alive
5	87	M	–	Cardiac condition Renal failure Multiple myeloma	60	2	28	Death

Table 3
Vaccine effectiveness (VE) against COVID-19 hospitalization among adults stratified in medical centers.

	VE (95% confidence interval)	*P*-value
VE after 1 dose (D1)		
D1 + 7D	79.1 ([67.0; 86.8]	< 0.001
D1 + 14D	84.0 [72.6; 90.6]	< 0.001
D1 + 21D	87.0 [76.0; 92.9]	< 0.001
D1 + 21D	88.3 [76.3; 94.2]	< 0.001
VE after 2 doses (D2)		
D2 + 7 D	96.2 [86.8; 98.9]	< 0.001
D2 + 14D	95.5 [84.1; 98.8]	< 0.001

odds of vaccinated patients hospitalized for the same symptoms but with a negative test.

VE and their 95% CIs were estimated using the formula VE = (1-OR) × 100. ORs were calculated by the exponentiated regression coefficients of vaccine status, stratified on medical center in the model using the logistic function in R. We estimated VE using various endpoints, from first dose + 7 days to second dose + 14 days. In univariate analysis, VE estimates ranged from 79.1% (95% CI = [67.0; 86.8]) 7 days after the first dose to 95.5% (95% CI = [84.1; 98.8]) 14 days after the second dose (Table 3).

To test result robustness, we performed various sensitivity analyses: one that requalified negative PCR tests to cases if COVID-19 diagnosis was recorded in medical files or if the CT-scan showed abnormalities suggestive of COVID-19 infection ($n = 46$ additional cases), and one using the WHO definition of severe acute respiratory infection (SARI) cases (defined by fever ≥ 38 °C and cough and onset within the past 10 days), which is more stringent ($n = 323$ inclusions). The overall results did not change and VE estimates after the second dose were 6% and 3% lower than in the main analysis, respectively (*i.e.* when requalifying negative PCR tests to cases in case of COVID-19 diagnosis as mentioned above and when using the WHO definition).

A generalized additional logistic regression model was used to adjust on other covariates: time, age, and stratified on centers. Time was measured in days between January 1, 2021 and hospitalization day. It was included as a spline function to account for bias related to time differences between COVID-19 circulation and vaccine availability. VE was estimated at 96.7% (95% CI = [87.9; 99.9]) 7 days after the second dose.

5. Discussion

Our results are in line with previous reports showing high COVID-19 VE to prevent hospitalizations, such as in the United-Kingdom, Israel and Qatar which showed > 90% effectiveness against severe forms, even against the B.1.1.7 variant (alpha), predominant in Qatar [3–6]. Moreover, our results are consistent with a previous cohort from Paris et al. and with a case control study in France from Charmet et al. to assess VE, which reported VE (95% CI) of 76% (54–87) and 84% (75–90) against COVID-19 with the original virus and the B.1.1.7 lineage (alpha variant), respectively [7,8]. However, the latter study had limitations: cases and controls came from two different databases, were not matched based on medical data, and were all declarative [8]. For our study, we prospectively collected clinical data at bedside, with detailed information on patients' hospitalization and careful selection of controls. We documented four hospitalized vaccine breakthrough infections, all in immunocompromised patients, in line with previous reports in kidney transplant recipients [9]. This is in line with data on HCWs reported in Israel [10]. While the epidemics is still ongoing, we carry on data collection and are generalizing whole-genome sequencing on a random sample of patients and in all vaccine breakthroughs. We believe our study will continue to provide interesting information on COVID-19. To address misclassification and selection biases, we performed sensitivity analyses, with no impact on results. Finally, we were not able at the time of analysis to sequence samples from all patients with documented COVID-19, but national data surveillance shows that the main circulating variant at the time of patient inclusion was the alpha variant [11].

6. Conclusion

Our results confirm the high effectiveness of COVID-19 vaccine in France to prevent hospitalizations due to the alpha variant during the first semester of 2021. Further data are expected to measure vaccine effectiveness against the delta variant.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

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Contribution of authors

Liem Binh Luong Nguyen: investigation, supervision, project administration, writing – original draft. Rebecca Bauer: formal analysis, data curation, visualization, methodology, writing – original draft. Zineb Lesieur: data curation, supervision, project administration, review & editing. Florence Galtier: investigation, supervision. Xavier Duval: investigation, supervision. Philippe Vanhems: investigation, supervision, review & editing. Fabrice Lainé: investigation, supervision, review & editing. Pierre Tattevin: writing – review & editing. Christine Durier: formal analysis, methodology, writing – original draft, review & editing. Odile Launay: funding acquisition, methodology, supervision, writing – original draft, review & editing.

Disclosure of interest

The authors declare that they have no competing interest.

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