BMC Infectious Diseases

RESEARCH

Open Access

Association between humoral serological markers levels and risk of SARS-CoV-2 infection after the primary COVID-19 vaccine course among ANRS0001S COV-POPART cohort participants

Mathieu Chalouni[1], Paul Loubet[2], Edouard Lhomme[1,3,4], Laetitia Ninove[5], Benoit Barrou[6], Jean-Yves Blay[7], Maryvonne Hourmant[8], Jérome de Seze[9], Martine Laville[10,11], Bruno Laviolle[12], Jean-Daniel Lelièvre[13], Jacques Morel[14], Stéphanie Nguyen Quoc[15], Jean-Philippe Spano[16], Benjamin Terrier[17], Anne Thiebaut[18], Jean-Francois Viallard[19], François Vrtovsnik[20], Sophie Circosta[21], Aude Barquin[1], Mariam Gharib[22], Eric Tartour[23], Béatrice Parfait[24], Rodolphe Thiébaut[1,3,4], Laurence Meyer[25], Xavier de Lamballerie[5], Odile Launay[2,26], Linda Wittkop[1,3,4*] and for the ANRS0001S COV-POPART study group

Abstract

Background We assessed the prognostic value of serological humoral markers measured one month after the last dose of the primary COVID-19 vaccine course for predicting the risk of severe acute respiratory syndrome coronavirus 2 SARS-CoV-2 infection over the following six months in specific populations.

Methods ANRS0001SCOV-POPART is a French nationwide multicenter prospective observational cohort study assessing the immune response to Covid-19 vaccines routinely administered to 11 subgroups of patients with chronic disease and a control group. Participants from the ANRS0001S COV-POPART were included if they received at least two doses of Covid-19 vaccine for the primary vaccine course, had measurements of anti-Spike, anti-receptor binding domain (RBD) IgG-specific or neutralizing antibodies one month after the end of the primary vaccine course, without being infected by SARS-CoV-2 before the measurement. SARS-CoV-2 infections defined by a positive PCR/antigenic test or seroconversion to detectable anti nucleocapsid antibodies were evaluated until the first COVID-19 booster injection. Cox proportional hazards models taking into account interval-censored data were implemented to estimate the association between each antibody level and the risk of SARS-CoV-2 infection. Predictive performances were evaluated by the area under the receiving operating characteristic curve (AUROC).

Results Two thousand five hundred seventy adults from a specific population and 1,123 from the control group were included. The cumulative probabilities of SARS-CoV-2 infections at five months after serological measurement were 6.0% 95% confidence interval: [5.0; 7.9] and 10.1% 95% confidence interval: [8.3; 11.9], respectively. Higher levels of anti-Spike IgG antibody were associated with a lower risk of SARS-CoV-2 infections in the control group, but not in

*Correspondence:
Linda Wittkop
linda.wittkop@u-bordeaux.fr
Full list of author information is available at the end of the article

the specific populations. Among the specific populations, AUROC were 74.5%, 74.9%, and 72.4% for anti-Spike IgG, anti-RBD IgG, and neutralizing antibodies, respectively. AUROC were superior in the specific populations, 82.0%, 81.2%, and 81.4% for anti-Spike IgG, anti-RBD IgG, and neutralizing antibodies, respectively.

Conclusions Vaccine-induced antibody response after the primary course of Covid-19 infection only moderately discriminated between participants developing a SARS-CoV-2 infection during the Omicron wave.

Trial registration NCT04824651 (first posted: 2021-04-01).

Keywords Specific populations, SARS-CoV-2, Vaccine, Prediction

Introduction

Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, several vaccines have been validated and recommended [1–3]. In France, the Covid-19 vaccination campaign started in December 2020, with BNT162b2 vaccine. In May 2021, three additional vaccines were available: mRNA-1273, ChAdOx1-nCoV19, and Ad26.COV2.S. For some specific populations a third dose in the primary vaccine course was recommended [4]. Booster injections were recommended from October 2021 onwards [5]. COVID-19 vaccines have been shown to reduce the risk of severe diseases, hospitalization, and death [6, 7]. Binding and neutralizing antibodies have been particularly studied as prognostic factors and potential correlates of protection [8–11]. However, these studies were essentially conducted in clinical trials evaluating the ChadOx1 nCoV-19 (AZD1222) and ARNm-1273 (Moderna) vaccines in a context where the predominant circulating variant was the alpha variant (B.1.1.7) [8, 12]. Other variants have emerged, in particular, the Omicron (B.1.1.529) variant and sub-variants, which are associated with a decreased vaccine efficacy [13], higher breakthrough infections, but decreased severity [14, 15] compared to previous variants or original strain. The current prognostic value of antibody levels in vaccinated populations is still not completely explored. In populations at risk of developing severe forms of SARS-CoV-2 infection, i.e. immunocompromised patients, Covid-19 vaccine effectiveness is lower than in the overall population [16, 17] and the role of the antibody response could be less important than the cellular response [18].

We aimed to evaluate the prognostic value of humoral serological markers levels, i.e. anti-Spike IgG, anti-receptor binding domain (RBD) IgG, and neutralizing antibodies, measured one month after the last dose received during the primary vaccine course for the risk of SARS-CoV-2 infection up to 6 months after the lase dose in the ANRS0001S COV-POPART cohort.

Methods

Study design

ANRS0001S COV-POPART cohort (NCT04824651, Registration Date: 03/25/2021) is a French nationwide multicenter prospective cohort study of specific populations (solid cancer, solid organs transplanted, hematopoietic stem cell transplant, chronic kidney disease and dialysis, systemic autoimmune diseases, inflammatory rheumatic disease, multiple sclerosis/neuromyelitis optica spectrum disorder, hypogammaglobulinemia, diabetic, obese non-diabetic, and persons with HIV receiving antiretroviral treatment) and a group without the above-mentioned chronic conditions. Participants older than 18 years, without known history of SARS-CoV-2 infection at inclusion were included between March 25th, 2021 to December 31st, 2021. The study design is further described in previous publications [5, 19]. Primary vaccine course choice was made according to the authorization, availability, national recommendations, and prescriber choice [4]. Visits to collect data on patient characteristics and samples for antibody measurements were scheduled before the first dose injection, at the time of the first, second, and third dose if any, and 6, 12, and 24 months after the second dose. Supplementary visits were implemented at the time and one month after a booster injection [19].

Study population

We included participants from the ANRS0001S COV-POPART who received at least two doses during the primary vaccine course (a third dose within the primary course was defined as an injection in a three-month window after the second dose), had at least one antibody value among anti-Spike IgG, anti-RBD IgG, or neutralizing antibodies one month after the last dose received during the primary vaccine course, and without SARS-CoV-2 infection before the antibody level measurement *(i.e. participants with positive anti-NCP antibodies or positive positive antigenic test or RT-PCR at baseline were not eligible).*

All analyses were implemented separately between participants from specific populations and the control group given the heterogeneity in antibody responses and the

usually lower antibody response in specific populations compared to the overall population [16, 17].

Antibody measurements

Antibody levels were measured one month (between 21 days and 56 days) after the last dose received during the primary vaccine course. The samples analyzed as part of the study were managed and stored within the « Biothèque ANRS ». All serological analyses were carried out centrally at the "Unité des virus émergents" Aix-Marseille Université, Institut de Recherche pour le Développement 190, Inserm 1207, Institut Hospitalo-Universitaire Méditerranée Infection, Marseille, France. Antibody assays used are described in the supplementary material (Supplementary materials antibodies measurement). For undetectable antibodies, half of the detection cut-off was imputed (15 BAU/mL and 10 IU/mL for anti-Spike IgG, and 10 Titers neutralizing antibodies, respectively).

We estimated the geometric means of the anti-Spike IgG, anti-RBD IgG, and neutralizing antibody titers measured one month after the last injection.

SARS-CoV-2 infection

SARS-CoV-2 infection was defined by a positive antigenic test or RT-PCR, positive anti-NCP antibodies, or an increase in anti-Spike IgG antibody levels in the absence of a booster injection or the prescription of monoclonal antibodies. Anti-NCP antibodies are systematically evaluated at each visit in all participants as are anti-Spike IgG antibody levels. In case of a positive antigenic or RT-PCR test performed outside the cohort protocol, participants were asked to consult within 72 h for a clinical examination and to implement the biological testing.

Statistical methods

Participants were followed from the antibody measurement one month after the primary vaccine course until the occurrence of a SARS-CoV-2 infection, a first booster injection, last follow-up visit available, or death.

For positive anti-NCP and increase in anti-Spike IgG, the exact time of infection was interval-censored. Thus, an interval-censoring analysis using Cox proportional hazard models were implemented to estimate the cumulative incidences of SARS-CoV-2 infection and plotted up to 5 months after the antibody measurement, according to the populations and to the antibody value terciles. The association between the antibody value terciles and the risk of infection was evaluated using log-rank tests.

Cox proportional hazards models were used to model the association between antibody levels and the risk of SARS-CoV-2 infection. Antibodies levels were included in univariable Cox proportional hazards models implemented for each antibody transformed using restricted cubic splines with two boundary knots and three interior knots at the quantiles of the antibody to take into account non-linearity. Then, age (in years), sex, body mass index (BMI) (in kg/m^2), and number of vaccine doses received during the primary vaccine course were added to the model. Models were stratified on the calendar month of the last received dose during the primary vaccine course (May 2021 and before, June 2021, July 2021, August 2021, and after) and on the specific populations. The effect of anti-Spike IgG on SARS-CoV-2 infections was presented for specific values (15 BAU/mL half of the level of detection and 264 BAU/mL identified as protective for the risk of infection post-vaccination [8]). The Hazard Ratios (HR) were estimated by dividing the probabilities of events estimated using the parameters from the multivariable model for each specific value (e.g. p(SARS-CoV-2 = 1, IgG = 264 BAU/mL) / (p(SARS-CoV-2 = 1, IgG = 15 BAU/mL)).

Predictive performances of the antibody measurements in univariable and multivariable analysis, and of a model without antibody measurement were evaluated at five months using a time-dependent area under the receiver operating characteristic (AUROC) [20] corrected for optimism by bootstrap [21].

Sensitivity analyses

To evaluate the robustness of our results, we implemented several sensitivity analyses. First, we estimated the association and the predictive abilities of the antibody values on the risk of SARS-CoV-2 infection after the outcome definition was modified to consider only positive antigenic test and RT-PCR.

Second, as participants who received three doses during the primary vaccine course were excluded as a third dose injection during the primary vaccine course was recommended for participants with lower immune response.

Third, we divided the specific populations into participants with a metabolic chronic condition (diabetic and/or obese), infectious disease (HIV), and other specific populations to take into account the difference in vaccine response [19] and risk of infection by populations.

The analysis was implemented using R 4.1.2, the package icenReg for the Cox proportional hazard model timeROC for the AUROC estimation.

Results

Characteristics of the study populations

Of 6,108 participants in the ANRS0001S COV-POPART cohort study, 3,693 were included, 2,570 in the specific populations, and 1,123 in the control group (Fig. 1). Most of the participants in the specific populations ended their primary vaccine course between 1st May and 31st June

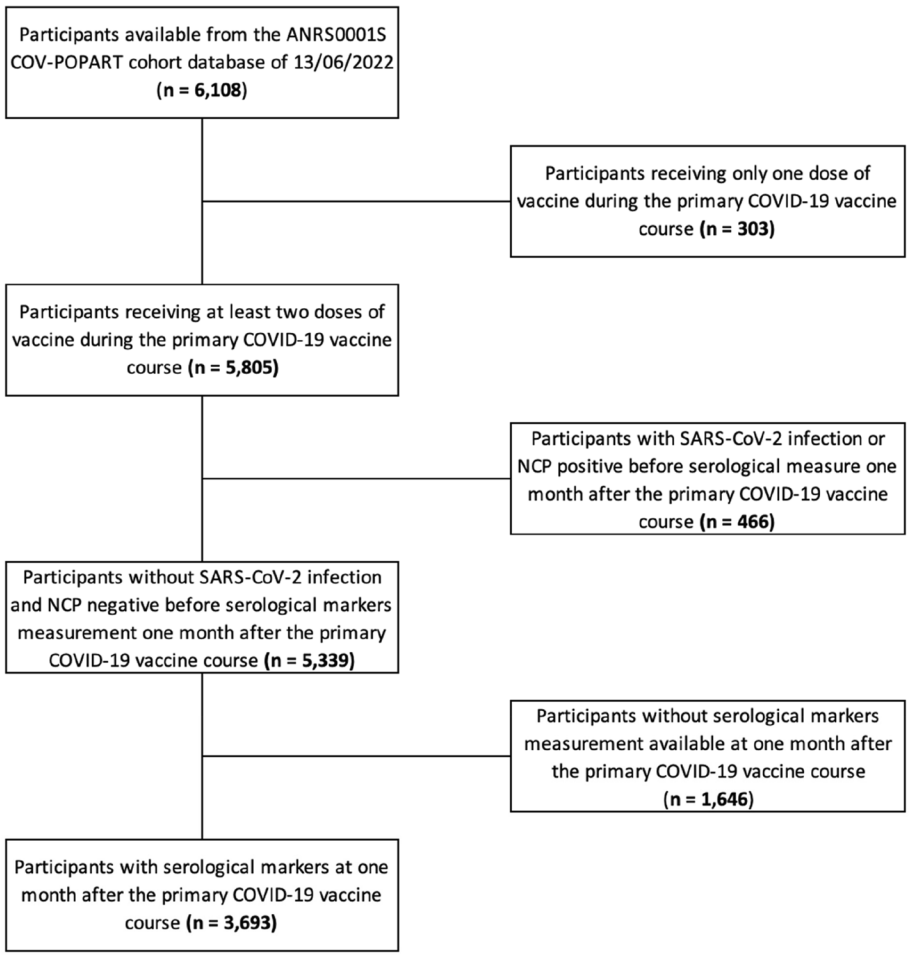

Fig. 1 Flowchart of the participants from the ANRS0001S COV-POPART cohort included in the study

2021 (71.8%) and between 1st June and 31st July 2021 (71.3%) for the control group. Participants in the specific populations were older (52.5 years interquartile range (IQR): [41.9; 61.0] vs. 47.4 [37.0; 57.8]) compared to the control group. Mainly prescribed primary vaccine course was two doses of BNT162b2 (81.8% and 84.4%, respectively). Of participants in specific populations, 33.3% were with HIV, 29.1% were obese non-diabetic, and 16.6% were diabetic, 7.5% received 3 doses in the primary vaccine course (Table 1).

Description of antibody responses

One month after the last dose received during the primary vaccine course the geometric means of anti-spike IgG, anti-RBD IgG, and neutralizing antibodies were 836.8 [789.7; 886.7] BAU/mL, 354.2 [330.8; 379.2] IU/mL and 139.4 [130.9; 148.5] titers, respectively in specific populations. In the control group, geometric mean concentrations were higher 1415.7 [1347.4; 1487.4] BAU/mL, 585.2 [555.8; 616.2] IU/mL and 317.1 [297.5; 337.9] titers, respectively [22] (Supplementary Tables 1 and Supplementary Fig. 1).

Description of SARS-CoV-2 infections

Over a median follow-up of 5.0 months [4.4; 5.8], 257 SARS-CoV-2 infections were observed, 143 (105 identified by antigenic test or PCR, 32 positive anti-NCP, and 6 increase in anti-Spike IgG antibody levels) in specific populations and 114 (99 identified by antigenic test or PCR, 13 positive anti-NCP, and 2 increase in anti-Spike IgG antibody levels) in the control group. During follow-up, 24 deaths were observed, all in participants from the specific populations. The majority of SARS-CoV-2 infections occurred in December 2021 (18.9% and 21.9%) or in January 2022 (39.2% and 50.0%), respectively in specific populations and in the control group. The cumulative probabilities at five months were 6.0% specific populations (95% confidence interval (CI): [5.0; 7.0]) and 10.1% in the control group (CI: 8.3; 11.9) (Supplementary Tables 2 and Supplementary Fig. 2).

Table 1 Characteristics at the end of the primary vaccine course in participants of the ANRS0001S COV-POPART cohort

Characteristics	Specific populations ($n=2570$)		Control group ($n=1123$)	
	N	**Median [IQR] or *n* (%)**	***N***	**Median [IQR] or *n* (%)**
Age (years)	2570	52.5 [41.9; 61.0]	1123	47.4 [37.0; 57.8]
< 65 years		2146 (83.3)		958 (85.3)
≥ 65 years		429 (16.7)		165 (14.7)
Men	2570	1324 (51.5)	1123	552 (49.2)
BMI (kg/m^2)	2570	25.6 [22.4; 31.1]	1123	23.6 [21.5; 26.0]
Population	2570		1123	
Solid cancer		172 (6.7)		-
Solid organs transplanted		70 (2.7)		-
Hematopoietic stem cell transplant		46 (1.8)		-
Chronic kidney disease and dialysis		75 (2.9)		-
Systemic autoimmune diseases		139 (5.4)		-
Inflammatory rheumatic disease		159 (6.2)		-
MS/NMOSD		363 (14.1)		-
Hypogammaglobulinemia		36 (1.4)		-
Diabetic		427 (16.6)		-
Obese non-diabetic		748 (29.1)		-
HIV		856 (33.3)		-
Number of doses in the primary vaccine course	2570		1123	
2		2378 (92.5)		1123 (100.0)
3		192 (7.5)		0 (0.0)
Type of vaccine	2564		1120	
BNT162b2 + BNT162b2		2098 (81.8)		945 (84.4)
BNT162b2 + BNT162b2 + BNT162b2		165 (6.4)		0 (0.0)
mRNA-1273 + mRNA-1273		226 (8.8)		99 (8.8)
AZD1222 + AZD1222		28 (1.1)		45 (4.0)
Others		47 (1.8)		31 (2.8)
Calendar period of last dose injection	2570		1123	
April 2021		134 (5.2)		25 (2.2)
May 2021		959 (37.3)		129 (11.5)
June 2021		885 (34.4)		425 (37.8)
July 2021		361 (14.0)		376 (33.5)
August 2021		130 (5.1)		117 (10.4)
September 2021		63 (2.5)		38 (3.4)
After September 2021		38 (1.5)		13 (1.2)
Monoclonal antibodies use	2570	19 (0.7)	1123	0 (0.0)
Other morbidities	2570		1123	
0		2079 (80.9)		1123 (100.0)
1		462 (18.0)		0 (0.0)
2		29 (1.1)		0 (0.0)

Control group: participants not from specific population of interest

Anti-SARS-CoV-2 antibody measurements and SARS-CoV-2 infection

The risk of SARS-CoV-2 infection was similar according to terciles of antibody markers in specific populations ($p=0.13$, 0.11, and 0.67, respectively for anti-Spike IgG, RBD, and neutralizing antibodies) and from the control group ($p=0.45$, 0.65, and 0.92, respectively for anti-Spike IgG, RBD, and neutralizing antibodies) (Fig. 2).

In the control group, after adjustment, higher levels of anti-Spike IgG antibody were associated with a lower risk of SARS-CoV-2 infection ($p=0.01$). The decrease in risk was more pronounced for lower values, but the

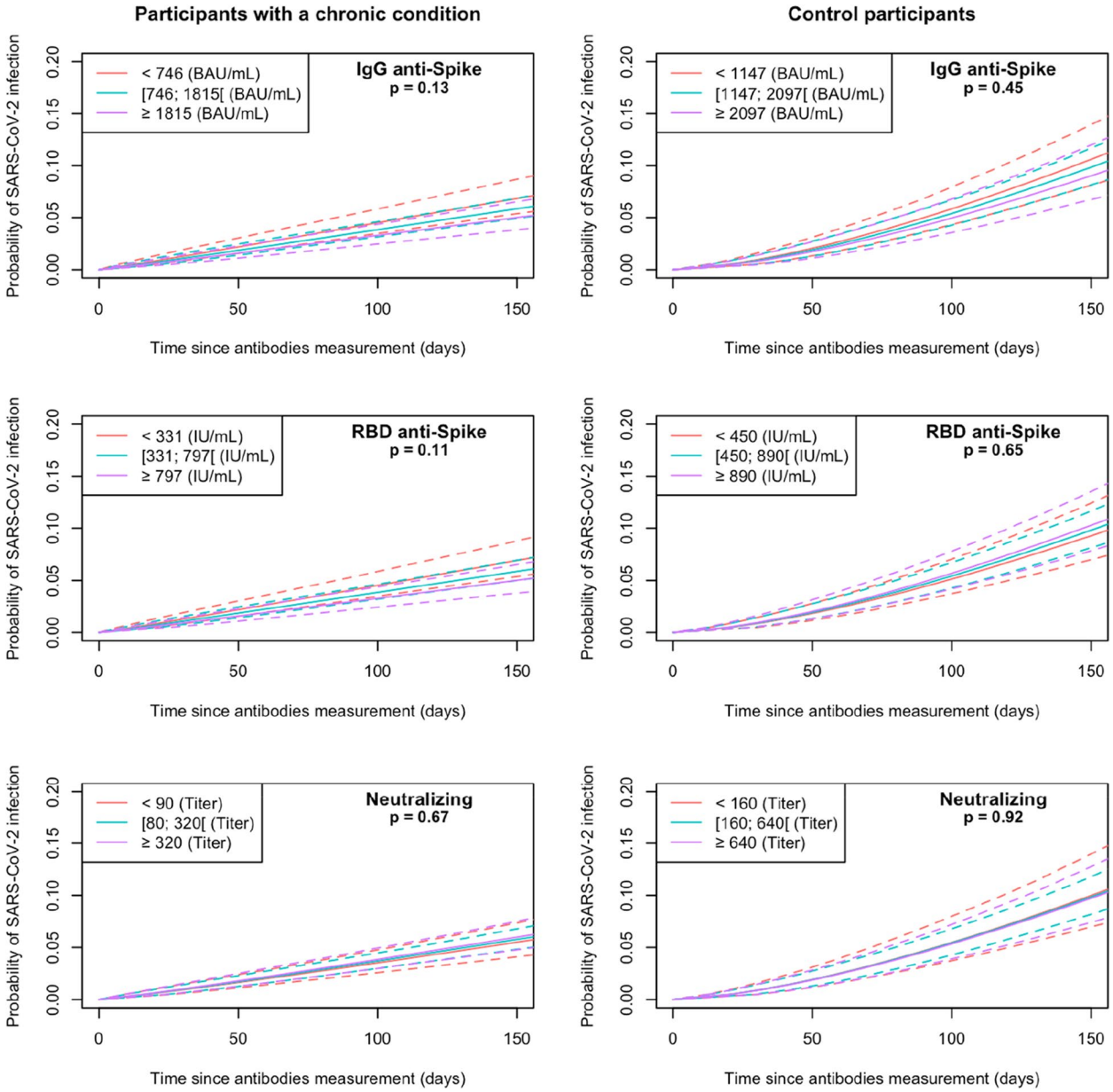

Fig. 2 Cumulative probabilities of SARS-CoV-2 infections from one month after the primary vaccine course according to the terciles of antibodies values in participants from the ANRS0001S COV-POPART cohort

P-values presented are from the log-rank tests for the global effect of antibodies categorized by terciles

risk continued to decrease for higher values of anti-Spike IgG (Fig. 3). Participants with a value of 264 BAU/mL of anti-Spike IgG antibodies had a lower risk of SARS-CoV-2 infection (HR: 0.4 [0.0; 0.9]) compared to a participant with a value of 15 BAU/mL. Risk of SARS-CoV-2 infection was not differentiated by neutralizing ($p=0.09$) and RBD IgG ($p=0.17$) antibodies (Fig. 3). In the specific populations, no associations between the antibody values and the risk of SARS-CoV-2 infection were estimated after adjustment ($p=0.15$, 0.22, 0.85, respectively for anti-Spike IgG, RBD, and neutralizing antibodies) (Fig. 3).

When SARS-CoV-2 infection was defined using only antigenic test and PCR, similar results were estimated with a decreased risk for participants with higher anti-Spike IgG value in the control group, and no association for other markers in both populations (Supplementary Table 3).

Predictive performances

In specific populations, the predictive performances of the three antibodies were moderate, with better performances for anti-Spike IgG (AUROC: 73.2%), then anti-RBD IgG (70.9%), and neutralizing antibodies (68.5%). The predictive performances of the multivariable models were slightly superior (74.5%, 74.9, and 72.4%, respectively for anti-Spike IgG, RBD IgG, and neutralizing antibodies), which were similar and superior to the one of a model without antibodies (67.0%). In the control group, the performances of the antibody were superior both in univariable (78.3%, 77.0%, and 78.8%, respectively for anti-Spike IgG, RBD IgG, and neutralizing antibodies) and in multivariable (82.0%, 81.2%, and 81.4%, respectively for anti-Spike IgG, RBD IgG, and neutralizing antibodies). However, the gain induced by the addition of the antibodies to the model was low (81.2%) (Table 2).

When defining SARS-CoV-2 infection based on antigenic test and RT-PCR only, the predictive abilities of the antibody values decreased and were similar in both populations (Anti-Spike IgG: 71.0% and 71.1%, anti-RBD IgG: 70.1% and 67.8%, Neutralizing antibodies: 66.7% and 68.8%, respectively in specific population and the control group) (Supplementary Table 5).

In specific populations who received two doses during the primary vaccine course, diabetic or obese, and other specific populations than diabetic, obese, and persons with HIV, the results were similar to the overall specific population. Among participants with HIV, the predictive performances were low both in univariable and multivariable analysis (Supplementary Table 6).

Factors associated with the risk of SARS-CoV-2 infections

After adjustment on IgG anti-Spike value, older age (HR: 0.8 [0.7; 0.9] and 0.7 [0.6; 0.8] for an increase of 10 years, respectively in specific populations and the control group) and being a woman (0.7 [0.5; 1.0] and 0.7 [0.5; 1.0], respectively) were significantly associated with a decreased risk of SARS-CoV-2 infection, in both specific populations and the control group. In specific populations, higher BMI (1.1 [1.0; 1.3] for an increase of 5 kg/m^2) was associated with an increased risk of SARS-CoV-2 infection (Supplementary Table 3). The same factors were identified when modifying the definition of SARS-CoV-2 infection (Supplementary Table 4).

Discussion

The cumulative probability of SARS-CoV-2 infection was low and mainly occurred after 1st December 2021, corresponding to the Omicron BA.1 wave in France. Higher anti-Spike IgG antibody levels at one month after the primary vaccine course was associated with a decreased risk of SARS-CoV-2 infection in the control group, but not in the specific populations. Our results indicate moderate performances of the antibody values to discriminate participants experiencing SARS-CoV-2 infection in the 5 months following the primary vaccine course in the specific populations, and good, but similar to the one of a model without antibody results in control participants.

We observed higher probabilities of SARS-CoV-2 infections in the control group, with a sharp increase at the end of the follow-up period, compared to specific populations. Participants from the specific populations may have engaged in less risky behavior than the general population. In participants with a lower antibody response, the role of the antibody response is less important than the cellular response [18]. In addition, all participants of the control group were responders with high antibody measurements at baseline. A progressive decrease in the protection could explain the infections observed at a later follow-up. Finally, due to the recommendation, participants in the control group received their booster injection later than participants from specific populations and were more exposed to the Omicron wave. The same factors could explain the decreased risk of SARS-CoV-2 with increasing age. As identified in previous studies, women [22, 23] were at lower risk, and participants with high BMI [24] were at higher risk of SARS-CoV-2 infection.

Increased anti-Spike IgG antibody level was associated with a decreased risk of SARS-CoV-2 infection in the control group. In the specific populations, antibody levels were not associated with the risk of SARS-CoV-2,

(See figure on next page.)

Fig. 3 Association between antibody values and risk of SARS-CoV-2 infections after the primary vaccine course in participants of the ANRS0001S COV-POPART cohort study

Models were adjusted on age, sex, BMI, number of doses and number of other morbidities and stratified by month of the last received injection during the primary vaccine course and the specific population in specific populations and age, sex and BMI in the control group. Dark line is the Hazard Ratio (HR) estimated by a Cox proportional hazards model and area between the dashed lines is the 95% confidence of the HR. The antibody value associated with the median probability of predicted events by the model served as the reference for estimating the HR. Values associated with the median probability were: 1470 BAU/mL,1687 IU/mL, and 640 titers in specific populations, and 2033 BAU/mL, 1524 IU/mL, and 320 titers in the control group, respectively. *P*-values of the associations: 0.15, 0.22, and 0.85 for anti-Spike IgG, RBD, and neutralizing antibody levels in specific populations, and 0.01, 0.17, and 0.09, respectively in the control group. Control group: participants not from specific populations

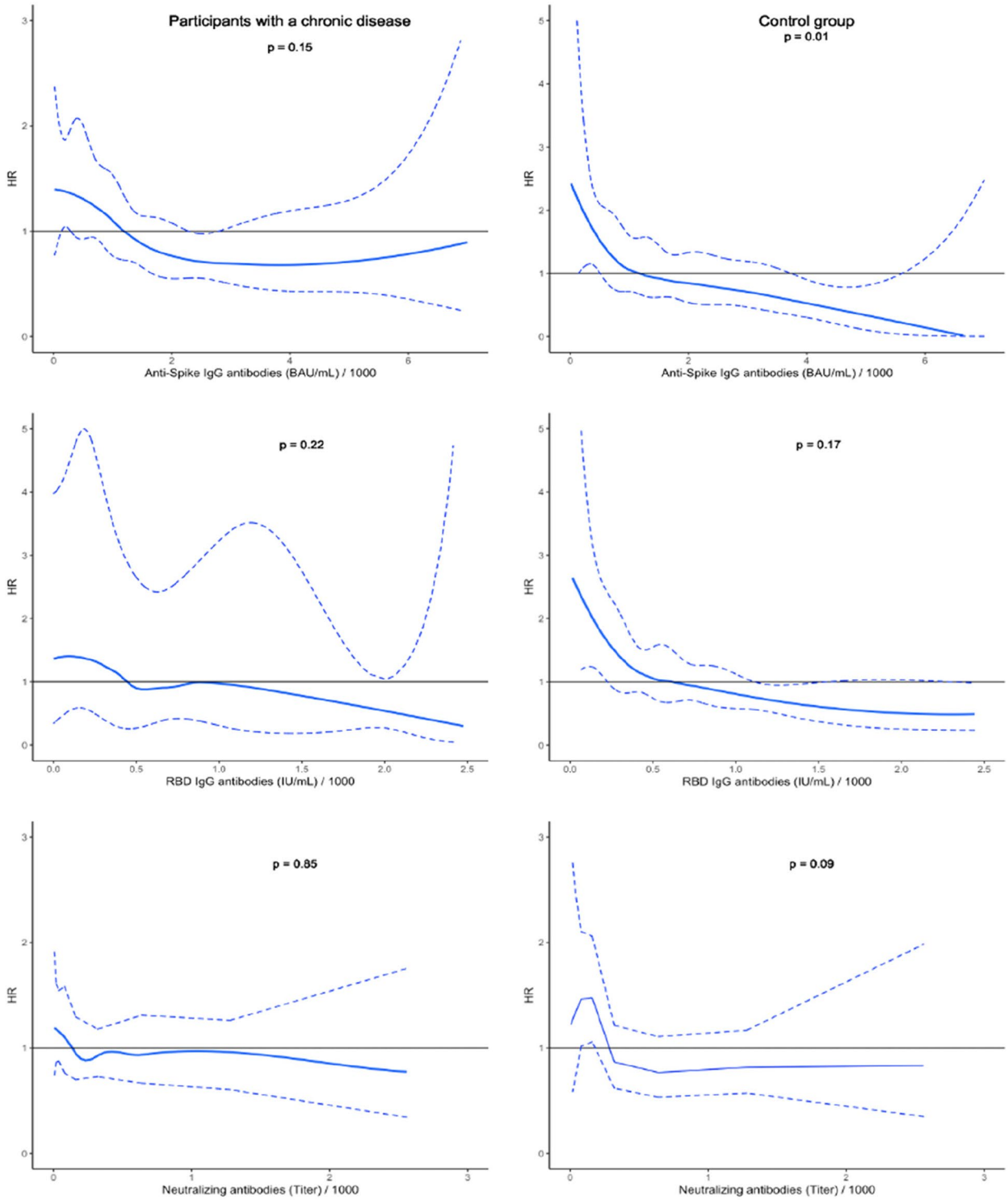

Fig. 3 (See legend on previous page.)

and their predictive abilities were moderate. The association between anti-spike IgG antibody level and the risk of SARS-CoV-2 infection has been previously published but differs for the RBD IgG and neutralizing antibody levels, which have been identified as potential correlates of protection [8, 12, 25–28]. This divergence could be explained

Table 2 Area under receiving operating characteristic (AUROC) of the antibody value for the prediction of SARS-CoV-2 infection at five months after baseline in participants from the ANRS0001S COV-POPART cohort

Antibodies	Specific populations		Control group	
	Univariable	Multivariable[a]	Univariable	Multivariable[b]
Anti-Spike IgG (BAU/mL)	73.2	74.5	78.3	82.0
Anti-RBD IgG (IU/mL)	70.4	74.9	77.0	81.2
Neutralizing antibodies (Titers)	68.5	72.4	78.8	81.4
Model without antibody	-	67.0	-	81.2

AUROC are corrected for optimism using 1000 bootstrap samples

Control group: participants not from specific populations

[a] Cox proportional hazards models adjusted on age, sex, BMI, number of doses and number of comorbidities and stratified by month of the last received injection during the primary vaccine course and the specific population

[b] Cox proportional hazards models adjusted on age, sex and BMI

by the differences with the previous studies which were realized using clinical trial data when the alpha-variant was predominant [8, 12], whereas this study presents data collected at the time of Omicron variant emergence which is associated with a decreased efficacy of vaccines [13, 29, 30]. The moderate predictive abilities do not question the role of these antibodies and their usefulness for the evaluation of the vaccine response. Especially since the humoral response after the primo-vaccination is less mature than after the booster injection [31].

This study has some limitations. We cannot study severe forms (i.e. hospitalization, intensive care, or mortality) of SARS-CoV-2 infections. In previous studies, antibodies were identified as correlates of protection for symptomatic SARS-CoV-2 infection [8, 12, 25]. For asymptomatic SARS-CoV-2 infection, similar associations were estimated before vaccination [32], but not after [8, 12, 25] which could explain why antibody levels were not predictive for SARS-CoV-2 infections in our analyses. Data about RT-PCR or antigenic test results were collected during visits made at the convenience of the participants and anti-NCP tests do not have a 100% sensitivity and wane over time [33]. Therefore, we cannot rule out that we missed asymptomatic SARS-CoV-2 infection.

Here, we focused on the abilities of the antibody measurements to predict the risk of SARS-CoV-2 infection before the booster injection when the immune response might not be mature yet and this might explain our results. A future study will evaluate the SARS-CoV-2 risk after booster injection. RBD-IgG and neutralizing antibodies for the Omicron variant are only measured on sub-samples of each subpopulation within the ANRS0001S COV-POPART study and given the low number of SARS-CoV-2 infection in the study period we could not explore this further.

In conclusion, in a context where the predominant variant was Omicron, the ability of antibody values to discriminate participants who will develop a SARS-CoV-2 infection after the primary vaccine course and before the 1st booster injection was moderate in the specific populations and good in the control group but similar to a model without SARS-CoV-2 antibodies. These results add to the existing body of evidence that people from specific populations might need more intensive primary vaccine schedules. Further studies including antibody measurements after the booster vaccination are need to study the role of antibody responses in people from specific populations with regard to the risk of SARS-CoV-2 infection.

Abbreviations

AUROC	Area under the receiver operating characteristic
CI	Confidence Interval
HIV	Human immunodeficiency virus
HR	Hazard Ratio
IQR	Interquartile range
SARS-CoV-2	Severe acute respiratory syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09861-5.

Supplementary Material 1. Antibodies measurement [34].

Authors' contributions

MC and LW: original draft; MC, PL, EL, LN, BB, JYB, MH, JS, ML, BL, JDL, JM, SNQ, JPS, BT, AT, JFV, FV, SC, ET, BP, RT, LM, XL, OL, and LW: writing – review and editing, conceptualization; PL, LN, BB, JUB, MH, JS, ML, BL, JDL, JM, SNQ, JPS, BT; AT, JFV, FV, SC, ET, BP, WL, and OL: investigation; LW and MC: methodology; LW and MC: formal analysis; PL, LW, MG, AB, ET, XL and OL: project administration. All authors read, revised, and approved the final manuscript.

Funding

The ANRS0001S COV-POPART cohort is sponsored by Inserm – ANRS MIE, conducted with the support of ANRS MIE and funded by French ministries (Ministère des Solidarités et de la Santé and Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation).

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from each participant before enrolment taking into account the GDPR (European Union General Data Protection Regulation) requirements. The protocol (N° EudraCT / ID-RCB: 2021-A00348-33) was conducted in accordance with the Declaration of Helsinki and French law for research involving human subjects (known as Loi Jardé). The protocol was approved by Ethics Committees: the committee for protection of participants engaged in research "CPP Nord-Ouest IV" (file number: 21.02.12.47147) and the French national data protection authority "CNIL" (Commission Nationale Informatique et Liberté, authorization number 921111v1).

Consent for publication
Not applicable.

Competing interests
PL has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astrazeneca, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Pfizer, Sanofi Pasteur and Support for attending meetings and/or travel from Pfizer, Sanofi Pasteur. JM has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Biogen, BMS, Boerhinger Ingelheim, Galapagos, GSK, Fresenius Kabi, Lilly, Mylan, Novartis, Pfizer, Sanofi and grants outside the submitted work from Lilly, Novartis. JPS has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer and Astrazeneca. OL has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi Pasteur; Pfizer, Janssen and, non-financial support from Sanofi Pasteur; Pfizer, Janssen, GlaxoSmithKline and grant from GlaxoSmithKline. The other authors declare having no conflict of interest.

Author details
[1]Université de Bordeaux, ISPED, INSERM, Bordeaux Population Health Research Center, U1219, Bordeaux F-33000, France. [2]INSERM, F-CRIN, Reseau Innovative Clinical Research in Vaccinology (IREIVAC), Paris, France; Service des Maladies infectieuses et Tropicales, CHU de Nîmes, Nîmes, France; INSERM U1047 - Université de Montpellier, Nîmes, France. [3]INRIA SISTM team, Talence, France. [4]Service d'Information médicale, CHU de Bordeaux, Bordeaux F-33000, France. [5]Unite des Virus Emergents, Aix-Marseille Université, Institut de Recherche pour le Développement 190, Inserm 1207, Institut Hospitalo-Universitaire Méditerranée Infection, Marseille, France. [6]Service de Transplantation Rénale, Pitié Salpêtrière, APHP, Sorbonne Université, Paris, France. [7]Centre Léon-Bérard, Département de cancérologie médicale, Lyon, France; Université Claude Bernard Lyon, Unicancer, Lyon, France. [8]Service de Néphrologie-Immunologie clinique, CHU Nantes, Nantes, France. [9]CIC INSERM 1434, Strasbourg university hospital, Strasbourg, France. [10]INSERM U1191/UMR 5203, Université de Montpellier, Montpellier, France. [11]CHU de Lyon, Université de Lyon, Association Française d'Etudes et de Recherche de l'Obésité, INSERM, F-CRIN -French Obesity Research Centre of Excellence (FORCE) Network, Lyon, France. [12]Université de Rennes, CHU Rennes, INSERM, CIC 1414, Rennes, France. [13]Vaccine Research Institute, INSERM et APHP, Hôpital H. Mondor, Créteil, France. [14]Département de Rhumatologie, CHU et Université de Montpellier, Montpellier, France. [15]Centre d'Immunologie et des Maladies Infectieuses-Paris, APHP-Sorbonne Université, INSERM U1135, CNRS ERL 8255, Paris, France. [16]INSERM, institut Pierre-Louis d'épidémiologie et de santé publique (IPLESP), équipe TheraVir, AP-HP, Sorbonne université, hôpital universitaire Pitié-Salpêtrière, Oncologie médicale, CLIP2 Galilée, Sorbonne université, Paris, France. [17]Service de Médecine Interne, Hôpital Cochin, APHP, Paris, France. [18]Département d'Hématologie, CHU Grenoble Alpes, Grenoble, France. [19]Université de Bordeaux, Hôpital Haut-Lévêque, Bordeaux, France. [20]Département Hospitalo-Universitaire Fire, Service de Néphrologie, Hôpital Bichat-Claude Bernard, APHP, Université de Paris, Paris, France. [21]INSERM, SC10-US019 Essais thérapeutiques et Maladies Infectieuses, Paris, France. [22]ANRS Maladies infectieuses émergentes (ANRS MIE), Paris, France. [23]Service d'Immunologie biologique, Hôpital européen Georges Pompidou/APHP, Paris, France. [24]Centre de ressources Biologiques, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Paris, France. [25]Université Paris Saclay, CESP Inserm U1018, APHP Service de Santé Publique, le Kremlin- Bicêtre 94276, France. [26]INSERM, F-CRIN, Reseau Innovative Clinical Research in Vaccinology (IREIVAC), Paris, France; Centre d'Investigation Clinique Cochin Pasteur, Hôpital Cochin/APHP, INSERM CIC 1417, Paris, France; Université de Paris, Paris, France.

Received: 31 May 2024 Accepted: 2 September 2024
Published online: 27 September 2024

References

1. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet Lond Engl. 2021;397(10269):99–111.
2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15.
3. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA. 2021;326(1):35–45.
4. Haute Autorité de Santé. Avis n° 2022.0004/AC/SESPEV du 13 janvier 2022 du collège de la Haute Autorité de santé relatif à la place du vaccin Janssen en seconde dose et en dose de rappel dans la stratégie de vaccination contre la Covid-19. Available from: https://www.has-sante.fr/jcms/p_3309607/fr/avis-n-2022-0004/ac/sespev-du-13-janvier-2022-du-college-de-la-haute-autorite-de-sante-relatif-a-la-place-du-vaccin-janssen-en-seconde-dose-et-en-dose-de-rappel-dans-la-strategie-de-vaccination-contre-la-covid-19. Cited 2023 Jan 17.
5. Loubet P, Wittkop L, Tartour E, Parfait B, Barrou B, Blay JY, et al. A French cohort for assessing COVID-19 vaccine responses in specific populations. Nat Med. 2021;27(8):1319–21.
6. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA et al. BNT162b2 mRNA Covid-19 vaccine in a Nationwide Mass Vaccination setting. N Engl J Med. 2021;384(15):1412–23.
7. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet Lond Engl. 2021;397(10287):1819–29.
8. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med. 2021;27(11):2032–40.
9. McMahan K, Yu J, Mercado NB, Loos C, Tostanoski LH, Chandrashekar A, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature. 2021;590(7847):630–4.
10. 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(7):1205–11.
11. Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. Vaccine. 2021;39(32):4423–8.
12. Gilbert PB, Montefiori DC, McDermott AB, Fong Y, Benkeser D, Deng W, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science. 2022;375(6576):43–50.
13. Pegu A, O'Connell SE, Schmidt SD, O'Dell S, Talana CA, Lai L, et al. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. Science. 2021;373(6561):1372–7.
14. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. Lancet Lond Engl. 2022;399(10323):437–46.
15. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 Omicron Wave compared with previous waves. JAMA. 2022;327(6):583–4.

16. Perry C, Luttwak E, Balaban R, Shefer G, Morales MM, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-hodgkin lymphoma. Blood Adv. 2021;5(16):3053–61.
17. Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, et al. Randomized Trial of a third dose of mRNA-1273 vaccine in transplant recipients. N Engl J Med. 2021;385(13):1244–6.
18. Goldblatt D, Alter G, Crotty S, Plotkin SA. Correlates of protection against SARS-CoV-2 infection and COVID-19 disease. Immunol Rev. 2022;310(1):6–26.
19. Loubet P, Wittkop L, Ninove L, Chalouni M, Barrou B, Blay JY, et al. One-month humoral response following two or three doses of mRNA Covid-19 vaccines as primary vaccination in specific populations in France: first results from the ANRS0001S COV-POPART cohort. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2022;S1198-743X(22):00522–5.
20. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Stat Med. 2013;32(30):5381–97.
21. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162(1):W1-73.
22. Liu C, Lee J, Ta C, Soroush A, Rogers JR, Kim JH, et al. Risk factors associated with SARS-CoV-2 breakthrough infections in fully mRNA-Vaccinated individuals: retrospective analysis. JMIR Public Health Surveill. 2022;8(5):e35311.
23. Yamal JM, Appana S, Wang M, Leon-Novelo L, Bakota E, Ye Y, et al. Trends and correlates of breakthrough infections with SARS-CoV-2. Front Public Health. 2022;10:856532.
24. Stefan N. Metabolic disorders, COVID-19 and vaccine-breakthrough infections. Nat Rev Endocrinol. 2022;18(2):75–6.
25. Aldridge RW, Yavlinsky A, Nguyen V, Eyre MT, Shrotri M, Navaratnam AMD, et al. SARS-CoV-2 antibodies and breakthrough infections in the virus watch cohort. Nat Commun. 2022;13(1):4869.
26. Cromer D, Steain M, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis. Lancet Microbe. 2022;3(1):e52-61.
27. Fong Y, McDermott AB, Benkeser D, Roels S, Stieh DJ, Vandebosch A, et al. Immune correlates analysis of the ENSEMBLE single Ad26.COV2.S dose vaccine efficacy clinical trial. Nat Microbiol. 2022;7(12):1996–2010.
28. Baerends EAM, Hvidt AK, Reekie J, Søgaard OS, Stærke NB, Raben D, et al. SARS-CoV-2 vaccine-induced antibodies protect against Omicron breakthrough infection. iScience. 2023;26(9):107621.
29. Martín Pérez C, Aguilar R, Jiménez A, Salmerón G, Canyelles M, Rubio R, et al. Correlates of protection and determinants of SARS-CoV-2 breakthrough infections 1 year after third dose vaccination. BMC Med. 2024;22(1):103.
30. Marking U, Havervall S, Norin NG, Bladh O, Christ W, Gordon M, et al. Correlates of protection and viral load trajectories in omicron breakthrough infections in triple vaccinated healthcare workers. Nat Commun. 2023;14(1):1577.
31. Chu L, Vrbicky K, Montefiori D, Huang W, Nestorova B, Chang Y, et al. Immune response to SARS-CoV-2 after a booster of mRNA-1273: an open-label phase 2 trial. Nat Med. 2022;28(5):1042–9.
32. Atti A, Insalata F, Carr EJ, Otter AD, Castillo-Olivares J, Wu M, et al. Antibody correlates of protection from SARS-CoV-2 reinfection prior to vaccination: a nested case-control within the SIREN study. J Infect. 2022;85(5):545–56.
33. Follmann D, Janes HE, Buhule OD, Zhou H, Girard B, Marks K, et al. Anti-nucleocapsid antibodies after SARS-CoV-2 infection in the blinded phase of the randomized, placebo-controlled mRNA-1273 COVID-19 Vaccine efficacy clinical trial. Ann Intern Med. 2022;175:1258–65.
34. Gallian P, Pastorino B, Morel P, Chiaroni J, Ninove L, de Lamballerie X. Lower prevalence of antibodies neutralizing SARS-CoV-2 in group O French blood donors. Antiviral Res. 2020;181:104880.

Publisher's note